4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 878

[Docket No. FDA-2023-N-3392]

RIN 0910-A126

Medical Devices; General and Plastic Surgery Devices; Classification of Certain Solid Wound Dressings; Wound Dressings Formulated as a Gel, Creams, or Ointment; and Liquid Wound Washes

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA, Agency, or we) are proposing to classify certain types of wound dressings and liquid wound washes containing antimicrobials and/or other chemicals (unclassified, preamendments devices) as solid wound dressings; wound dressings formulated as a gel, cream, or ointment; and liquid wound washes. FDA currently regulates these unclassified devices as devices requiring premarket notification (510(k) requirements), with the product codes FRO, GER, MGP, MGQ, and EFQ, but FDA intends to create new product codes for these proposed classifications upon finalization of this classification action. FDA is proposing to classify certain wound dressings and liquid wound washes containing antimicrobials with a high level of antimicrobial resistance (AMR) concern (i.e., medically important antimicrobials) into class III. In addition, FDA is proposing to classify certain wound dressings and liquid wound washes containing antimicrobials with a medium or low level of AMR concern and/or other chemicals, into class II (subject to special controls and 510(k) requirements).

DATES: Either electronic or written comments on the proposed rule must be submit by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The https://www.regulations.gov electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2023-N-3392 for "Medical Devices; General and Plastic Surgery Devices; Classification of Certain Solid Wound Dressings; Wound Dressings Formulated as a Gel, Creams, or Ointment; and Liquid Wound Washes." Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other

applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

FOR FURTHER INFORMATION CONTACT: Brandon Kitchel, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 4626, Silver Spring, MD 20993-0002, 301-796-6055, brandon.kitchel@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

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I. Executive Summary

A. Purpose of the Proposed Rule

FDA is proposing to classify certain unclassified, preamendments wound dressings and liquid wound washes containing antimicrobials and/or other chemicals into three separate classification regulations: (1) solid wound dressings; (2) wound dressings formulated as a gel, cream, or ointment; and (3) liquid wound washes. A list of examples of antimicrobials and a list of categories and examples of other chemicals contemplated by this proposed rule are found in table 2 and table 3, respectively. For solid wound dressings, the intended use is to cover and protect a wound, to absorb exudate, and to maintain appropriate moisture balance within the wound. For wound dressings formulated as a gel, cream, or ointment, the intended use is to maintain appropriate moisture balance within the wound. For liquid wound washes, the intended use is to mechanically irrigate and physically remove debris from external wounds. It is also to moisten solid wound dressings to maintain appropriate moisture balance within the dressing.

FDA currently regulates these unclassified devices[1] as devices requiring premarket notification (510(k) requirements), with the product codes FRO, GER, MGP, MGQ, and EFQ.[2] FDA intends to create new product codes for these proposed classifications upon finalization of this classification action.[3] This proposed classification is based, in part, on the recommendations of multiple General and Plastic Surgery Devices Panel meetings (held on November 27, 1998 (Ref. 1), August 25 and 26, 2005 (Ref. 2), and September 20 and 21, 2016 (Ref. 3)) regarding the classification of wound dressings, public comments received on such recommendations, FDA's experience with these wound dressings and liquid wound washes, and other available information.

As discussed further in this preamble, FDA believes that with clarification of intended use claims, wound dressings and liquid wound washes subject to this proposed rule, including those with antimicrobials, should be regulated only as "devices" and not as combination products.[4] These products, though perhaps previously identified as combination products, are within the scope of this classification. Additionally, wound dressings and liquid wound washes that do not contain a component that achieves a primary intended purpose of the product through chemical action within or on the body are considered devices, even if these products contain

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[1] We refer to these products as devices because of their device mode of action, although, as noted later in the document, many of the products with wound management claims, based on a broad interpretation of such claims, have previously been generally identified as combination products. As explained later in the document, one of the purposes of this rulemaking is to clarify the intended uses of these products for classification purposes, based on the recommendations of the General and Plastic Surgery Devices Panel, by proposing not to include broad "wound management" claims in product labeling and be clarified to reflect the specific functions discussed in this document (e.g., "to protect and cover a wound"). Products that continue to have broad wound management claims, which may be unclear or misleading or indicate an objective intent outside of the clarified intended uses, will not be covered by and benefit from this proposed rulemaking and classification. After this proposed rule is finalized and the classification becomes effective, such products could be subject to a different type of marketing authorization, depending on the product claims. For example, products containing antimicrobials that make certain wound managements claims may be considered combination products or drugs and regulated as such.

[2] FDA's Center for Devices and Radiological Health (CDRH) uses product codes to help categorize and assure consistent regulation of medical devices. A product code consists of three characters that are assigned at the time a product code is generated and is unique to a product type. The three characters carry no other significance and are not an abbreviation.

[3] See "Medical Device Classification Product Codes--Guidance for Industry and FDA Staff," available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/medical-device-classification-product-codes-guidance-industry-and-food-and- drug-administration-staff.

[4] See definition of combination product at 21 CFR 3.2(e).

components that are regulated as drugs in other contexts[5]. Further discussion of these products is included in the intended use(s) section under section V.B.

The proposed classification for solid wound dressings is intended to be a split classification. FDA is proposing to classify solid wound dressings containing medically important antimicrobials acting as protectants (Ref. 4)[6] into class III due to their high level of antimicrobial resistance (AMR)[7] concern (as discussed in Section III.B Terminology). Table 1 of the World Health Organization's (WHO) 2018 publication "Critically Important Antimicrobials for Human Medicine: 6th Edition" (Ref. 4) has a list of all classes of medically important antimicrobials. For the purposes of this proposed rule, an antimicrobial is considered medically important if, and only if, it falls within any of these classes regardless of the level of importance specified by the WHO (i.e., critically important, highly important, or important). FDA is proposing this classification as FDA believes that insufficient information exists to determine that general controls and special controls would provide reasonable assurance of safety and effectiveness for such wound dressings, and these dressings present a potential unreasonable risk of illness or injury. FDA is proposing, by proposed order published elsewhere in this issue of the *Federal Register*, to require the filing of premarket approval applications (PMAs) for such devices.

FDA is proposing to classify solid wound dressings containing antimicrobials that are acting as protectants with medium or low level of AMR concern and/or other chemicals into class II (special controls). Please see Section III.B Terminology for more information on

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[5] For information on the classification of products as drugs, devices, or biological products, please see the guidance "Classification of Products as Drugs and Devices and Additional Product Classification Issues," available at https://www.fda.gov/media/80384/download.

[6] For the purposes of this proposed rule and classification action, medically important antimicrobials are antimicrobial drugs that are important for therapeutic use in humans and associated with a high level of AMR concern. WHO has worked to categorize medically important antimicrobials based on the level of importance these drugs play in human medicine (https://www.who.int/publications/i/item/9789241515528). While the Agency has made similar efforts to categorize medically important antimicrobials, such as the work to address the use of medically important antimicrobial drugs in food-producing animals (https://www.fda.gov/media/172347/download?attachment), the current classification efforts do not attempt to further stratify the degree of importance of these antimicrobial drugs.

[7] For the purposes of this proposed rule and classification action, antimicrobial resistance is the ability of a microorganism (e.g., bacteria or fungi) to resist the effects of an antimicrobial.

antimicrobials that are acting as protectants and on other chemicals. Antimicrobials acting as protectants are used to reduce microbial growth within the dressing while in use or to provide an antimicrobial barrier to microbial penetration through the dressing. FDA is proposing this classification action based on the determination that general controls alone are not sufficient to provide reasonable assurance of the safety and effectiveness of these solid wound dressings, and there is sufficient information to establish special controls, in combination with general controls, to provide such assurance.

Similarly, FDA is proposing a split classification for wound dressings formulated as a gel, cream, or ointment. FDA is proposing to classify wound dressings formulated as a gel, cream, or ointment containing medically important antimicrobials acting as preservatives into class III due to their high level of AMR concern. FDA is proposing this classification as FDA believes that insufficient information exists to determine that general controls and special controls would provide reasonable assurance of safety and effectiveness for such wound dressings and that these dressings present a potential unreasonable risk of illness or injury. FDA is proposing, by proposed order published elsewhere in this issue of the *Federal Register*, to require the filing of PMAs for such devices.

FDA proposes to classify wound dressings formulated as a gel, cream, or ointment containing antimicrobials acting as preservatives (as discussed in Section III.B Terminology) with medium or low AMR risk and/or other chemicals into class II. Antimicrobials acting as preservatives are used to maintain shelf life for a nonsterile, single-use wound dressing or a multiple-use wound dressing for single patient use only with compromised sterility after opening and using for a defined period. FDA is proposing this action based on the determination that general controls alone are not sufficient to provide reasonable assurance of the safety and effectiveness of these wound dressings, and there is sufficient information to establish special controls, in combination with general controls, to provide such assurance.

FDA is also proposing a split classification for liquid wound washes. FDA is proposing to classify liquid wound washes containing medically important antimicrobials acting as preservatives into class III due to their high level of AMR concern. FDA is proposing this classification as FDA believes that insufficient information exists to determine that general controls and special controls would provide reasonable assurance of safety and effectiveness for such liquid wound washes and these washes present a potential unreasonable risk of illness or injury. FDA is proposing, by proposed order published elsewhere in this issue of the *Federal Register*, to require the filing of PMAs for such devices.

FDA is proposing to classify liquid wound washes containing antimicrobials acting as preservatives with medium or low level AMR concern and/or other chemicals into class II. FDA is proposing this classification action based on the determination that general controls alone are not sufficient to provide reasonable assurance of the safety and effectiveness of these wound washes and that there is sufficient information to establish special controls, in combination with general controls, to provide such assurance. Additionally, if this proposed rule is finalized, FDA plans to publish a notice in the *Federal Register* announcing its intent to exempt liquid wound washes containing water or 0.9 percent saline only, which do not contain antimicrobials, other chemicals, or animal-derived materials, from the requirements of submitting a 510(k), subject to certain limitations, under the Federal Food, Drug, and Cosmetic Act (FD&C Act).

B. Summary of the Major Provisions of the Proposed Rule

This rule proposes to classify certain of the following unclassified, preamendments wound dressings and liquid wound washes containing antimicrobials and/or other chemicals: (1) solid wound dressings; (2) wound dressings formulated as a gel, cream, or ointment; and (3) liquid wound washes. The proposed rule, if finalized, would establish the identifications and classifications for certain solid wound dressings; wound dressings formulated as a gel, cream, or ointment; and liquid wound washes.

The proposed classification action proposes to classify into class III and require the filing of a PMA for wound dressings and liquid wound washes (i.e., solid wound dressings; wound dressings formulated as a gel, cream, or ointment; and liquid wound washes) containing medically important antimicrobials used for preservative or protectant purposes. This proposed classification action proposes also to classify solid wound dressings containing antimicrobials acting as protectants with a medium or low level of AMR concern and/or other chemicals into class II. Wound dressings formulated as a gel, cream, or ointment and liquid wound washes containing antimicrobials acting as preservatives with a medium or low level of AMR concern and/or other chemicals are being proposed for classification into class II. These certain class II wound dressings and liquid wound washes would be classified with special controls that require specific information relating to performance testing and technical specifications, specific labeling requirements, and other requirements to mitigate the risks to health and demonstrate a reasonable assurance of safety and effectiveness, in combination with general controls.

If this proposed rule is finalized, FDA plans to exempt from 510(k) certain liquid wound washes containing water or 0.9 percent saline only, which do not contain antimicrobials, other chemicals, or animal-derived materials, subject to certain limitations. An exemption from the requirement of 510(k) does not mean that the device type is exempt from any other statutory or regulatory requirements unless such exemption is explicitly provided by order or regulation.

C. Legal Authority

The Agency is proposing this classification under the authority of section 301 of the FD&C Act (21 U.S.C. 301). Specifically, the relevant authority related to the proposed classification includes sections 513(a) through (d) of the FD&C Act regarding device classes, classification, and panels; section 515 of the FD&C Act regarding PMAs; and section 701(a) of the FD&C Act (21 U.S.C. 371(a)).

D. Costs and Benefits

If the proposed rule is finalized, society may experience welfare gains from reductions in AMR due to the rule. These welfare gains would be in the form of decreased mortality, morbidity, and medical costs. Unfortunately, the magnitude of these potential benefits is difficult to forecast, and we do not quantify these impacts in the analysis.

The quantifiable benefits of the proposed rule, if finalized, accrue to manufacturers of wound dressings and liquid wound washes and FDA. These benefits are the result of clarifications in the 510(k) submission process, specifically defined regulatory classification, and published special controls. This additional clarity in requirements should result in fewer additional information submissions to FDA.

We estimate annualized cost savings ranging from approximately $1.12 million to $6.31 million at a 3 percent discount rate, and approximately $1.14 million to $6.42 million at a 7 percent discount rate. Our primary annualized estimates are approximately $2.66 million at a 3 percent discount rate and $2.71 million at a 7 percent discount rate. The primary estimates of the present value of total cost savings in the 10 years following any final rule that may be issued based on this proposed rule are $24.55 million at a 3 percent rate of discount and $19.02 million at a 7 percent rate of discount.

The costs of the proposed rule, if finalized, are associated with costs to industry for reading and understanding the rule, preparing and submitting PMAs, and other costs related to the PMA process and maintaining the class III designation. FDA also incurs costs from reviewing PMAs, annual and supplemental reports, and inspection activities. When annualized over a period of 10 years, we estimate these costs range from approximately $0.72 million to $1.25 million at a 3 percent discount rate, and approximately $0.65 million to $1.17 million at a 7 percent discount rate. Our primary annualized estimates are approximately $0.92 million at a 3 percent discount rate and $0.85 million at a 7 percent discount rate. The primary estimates of the present value of total costs in the 10 years following any final rule that may be issued based on

the proposed rule are approximately $7.23 million at a 3 percent discount rate and $6.48 million at a 7 percent discount rate.

II. Table of Abbreviations/Acronyms Commonly Used Acronyms in This Document

Abbreviation/Acronym	What It Means
510(k)	Premarket Notification
AMR	Antimicrobial Resistance
CDC	Centers for Disease Control and Prevention
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
FRO	The current product code for unclassified, preamendments wound dressings containing antimicrobials and/or other chemicals[8]
GER	The product code for unclassified, preamendments devices known as external gauze with drug/biologic/animal source material.[9]
MGP	The product code for unclassified, preamendments devices known as occlusive wound and burn dressing.[10]
MGQ	The product code for unclassified, preamendments devices known as wound and burn hydrogel dressing with drug and/or biologic.[11]
EFQ	The product code for unclassified, preamendments devices known as internal gauze and sponge.[12]
HHS	Department of Health and Human Services
PHMB	Polyhexamethylene Biguanide
PMA	Premarket Approval Application
OIRA	Office of Information and Regulatory Affairs
U.S.	United States
WHO	World Health Organization

III. Background

A. Need for the Regulation

Currently, certain solid wound dressings; wound dressings formulated as a gel, cream, or ointment; and liquid wound washes that contain antimicrobials and/or other chemicals are unclassified devices subject to premarket notification (510(k)) under section 510(k) of the FD&C Act (21 U.S.C. 360(k)). Until an unclassified device type has been formally classified by

[8] Some products cleared under this product code are within scope for this proposed rule and proposed classification action. Other products under this product code are not within scope of this proposed rule and will be addressed via a separate classification action.
[9] Ibid.
[10] Ibid.
[11] Ibid.
[12] Ibid.

regulation, and such formal classification may or may not require a different type of premarket submission depending on the classification, marketing of new devices within this device type requires FDA clearance of a 510(k). As described below, these devices have generally been subject to premarket review through the 510(k) pathway and have been cleared for marketing if their intended use and technological characteristics are "substantially equivalent" to devices that were in commercial distribution prior to the passage of the Medical Device Amendments on May 28, 1976.

Wound dressings and liquid wound washes subject to this proposed rule and classification action can be subcategorized into three broad categories based on their physical form, including: (1) solid wound dressings; (2) gels, creams, or ointments; and (3) liquid wound washes. Irrespective of physical form, these wound dressings and liquid wound washes have typically been indicated for use on a variety of acute (e.g., traumatic wounds, surgical wounds, etc.) and chronic (e.g., venous stasis ulcers, diabetic foot ulcers, arterial ulcers, etc.) wounds. Solid wound dressings have also been cleared with uses such as to provide or support a moist wound environment, absorb wound exudate, and protect against external contamination. Wound gels, ointments, and creams have been cleared to provide or support a moist wound environment. Liquid wound washes have been cleared to rinse or irrigate a wound and to remove foreign material, such as debris and wound exudate. Refer to table 1 for a tabular overview of the wound dressings and liquid wound washes within the scope of this proposed classification action.

Table 1.--Proposed Classification of the Wound Dressings and Liquid Wound Washes Containing Antimicrobials and/or Other Chemicals

Proposed Classification	Solid Wound Dressings Containing Antimicrobials and/or other Chemicals (Proposed New 21 CFR 878.4016)	Wound Dressings Formulated as a Gel, Cream, or Ointment Containing Antimicrobials and/or other Chemicals (Proposed New 21 CFR 878.4017)	Liquid Wound Washes (Proposed New 21 CFR 878.4019)
Class III (Proposing to require the filing of a PMA)	Products containing medically important antimicrobials acting as protectants (Proposed § 878.4016(b)(1))	Products containing medically important antimicrobials acting as preservatives (Proposed § 878.4017(b)(1))	Products containing medically important antimicrobials acting as preservatives (Proposed § 878.4019(b)(1))
Class II	Products containing	Products containing	Products containing

(Special Controls + General Controls) Subject to 510(k) Requirements	antimicrobials acting as protectants with a medium or low level of AMR concern, and/or other chemicals (Proposed § 878.4016(b)(2))	antimicrobials acting as preservatives with a medium or low level of AMR concern, and/or other chemicals (Proposed § 878.4017(b)(2))	antimicrobials acting as preservatives with a medium or low level of AMR concern, and/or other chemicals (Proposed § 878.4019(b)(2))

Outside of the scope for this rulemaking, FDA has previously classified certain wound dressings (which have similar intended uses as the products in scope for this proposed rule, but do not contain antimicrobials or other chemicals) as class I and exempt from 510(k) requirements (see 21 CFR 878.4014, 878.4018, 878.4020, and 878.4022). FDA has also previously determined wound dressings intended to accelerate the normal rate of wound healing that serve as a replacement for full-thickness skin grafting (e.g., artificial skin substitute) or treat full-thickness (i.e., third degree) burns to be class III medical devices. An example of a class III wound dressing is the Integra Omnigraft Dermal Regeneration Matrix that was approved through PMA P900033[13]. In addition to wound care products regulated by Center for Devices and Radiological Health (CDRH), the Center for Drug Evaluation and Research regulates certain drugs used in wound care, such as silver sulfadiazine cream indicated for the prevention and treatment of wound sepsis,[14] and the Center for Biologics Evaluation and Research regulates certain wound care products, such as the OrCel Bilayered Cellular Matrix composed of human allogeneic skin cells (PMA P010016)[15].

Wound dressings and liquid wound washes containing antimicrobials and/or other chemicals play a critical role in wound care for patients in the United States. Human skin wounds pose substantial risks to patients and increasing challenges to the U.S. public health (Ref. 5). The prevalence rate for chronic, nonhealing wounds is ~2 percent of the general population (Ref. 6). This prevalence rate is similar to that of heart failure, but unlike heart

[13] FDA Premarket Approval, Integra Omnigraft Dermal Regeneration Matrix, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P900033S042
[14] Drugs at FDA, Silver Sulfadiazine Cream, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/017381s053lbl.pdf.
[15] FDA Premarket Approval, OrCel™ (Bilayered Cellular Matrix), https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P010016.

failure, little is known regarding the outcome of these patients or the comparative effectiveness of the treatment they receive (Ref. 7). An aging population and its requisite medical interventions, the continuing rise in diabetes and obesity, and the increase in traumatic wounds all translate to large increases in skin wounds needing treatment (Refs. 6 and 8). Patients with the hardest to heal wounds include those with diabetes, obesity, sickle cell ulcers, vasculitis, and scleroderma (Refs. 6 and 8).

The cost of wound care in the United States alone exceeds $50 billion annually (Refs. 9-12). It is estimated that chronic, nonhealing wounds affect approximately 6.5 million people annually in the United States (Ref. 13). Often, these wounds become infected, interrupting and delaying wound healing and leading to increased treatment times, suffering, risk of severe complications, and expenses (Ref. 14). The annual wound care products market is expected to reach $22 billion by 2024, which demonstrates the magnitude of their impact on public health (Ref. 15).

B. Terminology

1. Medically Important Antimicrobial

For the purposes of this proposed rule and this classification action, the term "medically important" antimicrobial refers to an antimicrobial drug that is important for therapeutic use in humans (Ref. 16). Table 1 of the WHO's 2018 publication entitled "Critically Important Antimicrobials for Human Medicine: 6th Edition" (Ref. 4) has a list of all classes of medically important antimicrobials. For the purposes of this proposed rule and classification action, an antimicrobial is considered medically important if, and only if, it falls within any of these classes regardless of the level of importance specified by the WHO (i.e., critically important, highly important, or important).

2. High, Medium, and Low AMR Concern

For the purposes of this proposed rule and this classification action, the level of AMR concern has been defined based on the following antimicrobial characteristics:

- High-level of AMR concern results from wound dressings and liquid wound washes that contain a medically important antimicrobial as these products may directly contribute to the development and spread of organisms in the patient that are resistant to medically important antimicrobials, potentially further limiting a clinician's therapeutic options.
- Medium-level AMR concern results from wound dressings and liquid wound washes that contain a nonmedically important antimicrobial which may indirectly select for organisms with medically important antimicrobial resistance mechanisms via coselection mechanisms such as coresistance and cross-resistance[16].
- Low-level AMR concern results from wound dressings and liquid wound washes that contain a nonmedically important antimicrobial which lacks the ability to coselect for organisms with medically important antimicrobial resistance mechanisms. As microbial resistance mechanisms are constantly evolving, the categorization of low level of AMR concern for a particular antimicrobial may be upgraded to a medium level of AMR concern based on future emerging resistance information, such as evidence of coresistance or cross-resistance to medically important antimicrobials.

3. Antimicrobials as Preservatives or Protectants

To be within the scope of this proposed rule and classification action, antimicrobials could only be included within these wound dressings and liquid wound washes for two functions or roles to support the use of the dressing or wash: (1) a preservative or (2) a protectant of the product.

For the purposes of this proposed rule and proposed classification action, an antimicrobial is considered a preservative when added to wound dressings formulated as a gel, cream, or ointment and liquid wound washes solely to prevent or reduce contamination or

[16] Coresistance occurs when there are different resistance determinants present on the same genetic element. Cross-resistance occurs when the same genetic determinant is responsible for resistance to multiple types of antimicrobials, such as antibiotics and metals. *See* Baker-Austin C., M. Wright, R. Stepanauskas, et al., "Co-Selection of Antibiotic and Metal Resistance," *Trends in Microbiology*, 14(4), 2006. Available at https://www.cell.com/trends/microbiology/fulltext/S0966-842X(06)00051-5.

deterioration thereof while in its packaging during shelf storage.[17] This preservative role helps maintain product integrity and safety throughout a defined shelf life and/or use life. A preservative may be included in wound dressings formulated as a gel, cream, or ointment or liquid wound washes when there is a scientific need for the inclusion of the preservative. For example, preservatives may be needed when the product is provided to the user nonsterile, or when the product is provided as a sterile single-patient, multiple-use product which contains a preservative to reduce microbial growth in the product over a specified period after the sterile seal has been broken. In these situations, the preservative may be used to maintain sufficiently low bioburden and to prevent or retard deterioration of the product prior to application of the wound dressings formulated as a gel, cream, or ointment or liquid wound washes.

Antimicrobials that are not used solely to support the use of the wound dressings formulated as a gel, cream, or ointment or liquid wound washes by preventing or reducing contamination or deterioration thereof while in its packaging, or those in which the use is not scientifically needed, are not considered preservatives for the purposes of this proposed rule. As discussed later, other uses, such as delivery of antimicrobials to the wound, suggest an intent for the treatment of infection, which is generally achieved through chemical action within or on the wound and may not fall under CDRH's jurisdiction. Additionally, as solid wound dressings are generally provided as sterile, single-use products, the inclusion of antimicrobial preservatives in solid wound dressings would not be necessary.

For the purposes of this proposed rule and proposed classification action, an antimicrobial is considered a protectant when added to a solid wound dressing to prevent or reduce contamination or deterioration of the dressing while in contact with the wound. This protectant role supports the use of solid wound dressings (i.e., to cover and protect a wound, absorb exudate, and maintain appropriate moisture balance within the wound) throughout a

[17] Based on FDA's experience, in rare occasions, an antimicrobial may be added to a sterile, single-use amorphous wound dressing as a manufacturing aid to reduce bioburden prior to the manufacturing of the final, finished device.

defined use life. A protectant may be included in solid wound dressings when there is a scientific need for the inclusion of the protectant (e.g., solid wound dressings which may be applied to a wound for a period of multiple days and the dressing may be susceptible to microbial colonization and biofouling). FDA is unaware of a clinical need for including a protectant in wound dressings formulated as a gel, cream, or ointment or liquid wound washes, as an application of these products is not designed to remain on the body for sufficient time to justify clinical concern with microbial colonization of the product. Refer to table 2 for a tabular overview of examples of antimicrobials that are within the scope of this proposed classification action.

Table 2.--List of Examples of Antimicrobials* That Are Within the Scope of the Proposed Rule and the Proposed Classification Action for Certain Wound Dressings and Liquid Wound Washes

Antimicrobials with High-Level AMR Concern*	Antimicrobials with Medium-Level AMR Concern	Antimicrobials with Low-Level AMR Concern
Polymyxin B	Silver	Parabens
Silver sulfadiazine	Zinc	Hypochlorous acid
Bacitracin	Copper	Peroxide
	Chlorhexidine	Polyhexamethylene biguanide (PHMB)
	Benzalkonium chloride	Iodine

*As identified in the WHO's "Critically Important Antimicrobials for Human Medicine," Polymyxin B falls within the Polymyxcin class of medically important antimicrobials, Silver sulfadiazine falls within the Sulfonamide class of medically important antimicrobials, and Bacitracin falls within the Cyclic polypeptide class of medically important antimicrobials.

4. Other Chemicals

Wound dressings and liquid wound washes may contain other chemicals. Categories of other chemicals are wound protectants, honey, synthetic peptides, or botanical extracts. For the purposes of this proposed rule and proposed classification action, these ingredients are grouped as "other chemicals" and are only used to contribute to the uses of wound dressings and liquid wound washes by physical means (see table 3). Ingredients that achieve their primary intended purposes through chemical action would not fall under "other chemicals" for purposes of this proposed rule and proposed classification action and are therefore outside its scope.

- *Wound protectants*[18]. Wound dressings may contain wound protectants that provide a physical barrier to the external environment and help maintain moisture balance within the wound.
- *Honey*. Wound dressings may contain honey, which helps maintain moisture balance within the dressing.
- *Synthetic Peptides*. Wound dressings may include synthetic peptides, which are used to create a fibrous scaffold and provide physical structure to the wound dressing.
- *Botanical extracts*. Wound dressings may contain botanical extracts, which have such uses as to help maintain moisture balance within the dressing (e.g., as moisturizers, humectants, or emollients) and contribute to the physical structure of the dressing (e.g., as thickeners, emulsifiers, or stabilizers). A botanical extract is often a complex mixture of vegetable matter obtained from plants, algae, macroscopic fungi, and/or combinations of these species. For the purposes of this proposed rule, plant-derived materials that are highly purified (e.g., cellulose) or well-characterized (e.g., cotton) are not considered as other chemicals.

Table 3.--Categories and Examples of Other Chemicals That Are Within the Scope of the Proposed Rule and the Proposed Classification Action for Certain Wound Dressings

Categories of Other Chemicals	Examples of Other Chemicals
Wound Protectants	Petrolatum, mineral oil, cod liver oil, white petrolatum, lanolin, glycerin, dimethicone, lanolin, allantoin, zinc oxide, aluminum hydroxide, calamine, sodium bicarbonate, zinc acetate, zinc carbonate
Honey	Manuka honey, buckwheat honey

[18] Ingredients in the "wound protectant" category of "other chemicals" overlap in some cases with active ingredients included in the over-the-counter (OTC) drug product monograph for "skin protectant drug products," which was codified in 21 CFR part 347. These provisions now appear in the final order for skin protectant drug products under section 505G of the FD&C Act (21 U.S.C. 355g), which was added by the Coronavirus Aid, Relief, and Economic Security Act, Pub. L. No. 116-136, 134 Stat. 281 (2020). Orders for OTC monograph drugs can be found at https://dps.fda.gov/omuf. Under section 3621 of the Food and Drug Omnibus Reform Act of 2022, Pub. L. No. 117-328, 136 Stat 4459, which added section 503(h) to the FD&C Act (21 U.S.C. 353(h), products meeting the definition of "OTC monograph drug" under section 744L of the FD&C Act (21 U.S.C. 379j-71), including certain skin protectants, are deemed to be drugs. When intended for marketing in accordance with this proposed rule, however, products containing these ingredients, which may be included as "wound protectants," would not be considered OTC monograph drugs or otherwise considered drug constituent parts. Please note that to be considered a "wound protectant" in accordance with this proposed rule and classification action, an ingredient cannot achieve its primary intended purpose through chemical action. Products containing such ingredients are outside the scope of this proposed rule and classification action.

Synthetic Peptides	RADA16 (RADARADARADARADA) peptide, self-assembling peptides
Botanical Extracts	Olive oil, grape seed extract, aloe, lavender, tea tree oil, vegetable oil, shea butter, sesame oil

5. Animal-Derived Materials

Solid wound dressings, wound dressings formulated as a gel, cream, or ointment, and liquid wound washes may also contain animal-derived materials. Generally, these animal-derived dressing materials are degradable, but may also contain nondegradable materials. This proposed rule excludes wound dressings and liquid wound washes containing animal-derived materials without the presence of antimicrobials or other chemicals, as these products are currently regulated as a distinct category under the product code KGN. More information regarding the categories of wound dressings and liquid wound washes that are outside the scope of this rulemaking is included in Section V.A Scope/Applicability of this proposed rule.

6. Antimicrobial Resistance

In the past century, the discovery and implementation of medically important antimicrobials (e.g., antibiotics) have revolutionized modern medicine, making once lethal infections readily treatable and extending the average human lifespan by 23 years (Ref. 17). Unfortunately, we now live in an era when people are dying from untreatable infections because of the emergence and spread of AMR--the ability of microorganisms (e.g., bacteria and fungi) to resist the effects of an antimicrobial. The development and spread of AMR are widely recognized as a serious public health threat. According to the U.S. Centers for Disease Control and Prevention (CDC), drug-resistant bacteria cause more than 35,000 deaths and 2.8 million illnesses each year in the United States (Ref. 18). In addition to the impact on patient morbidity and mortality, AMR infections require prolonged and costlier treatments, with estimates suggesting the U.S. economic impact to be around $55 billion per year (Ref. 19).

With a lack of novel antibiotics being developed, it is critical to preserve the effectiveness of our current antimicrobial therapeutic options. Based on the 2016 National Quality Partners' "Antibiotic Stewardship in Acute Care: A Practical Playbook" (Ref. 20), 20

percent to 50 percent of antibiotics prescribed in U.S. acute care hospitals are unnecessary or inappropriate, and this overuse and misuse of medically important antimicrobials have contributed to the cultivation of an abundance of drug-resistant organisms that are becoming increasingly difficult to treat. Changes to clinical practice patterns to promote appropriate use of antimicrobial drugs are essential, and in 2014, the CDC called on all U.S. hospitals to implement antimicrobial stewardship programs (Ref. 21) that measure and improve how antimicrobials are prescribed and used by patients. Additionally, public health agencies in the Department of Health and Human Services, including FDA, are engaged in efforts to promote antimicrobial stewardship practices to maintain a more judicious use of antimicrobials and curb the spread of AMR (Ref. 22).

While an antimicrobial is effective when applied at an appropriate concentration, this effectiveness is only exhibited on a limited segment of the microbial world. Some species of bacteria are naturally resistant to a given antimicrobial, while others may eventually acquire resistance (e.g., via random mutation or acquisition of a resistance gene) (Ref. 23). After decades of antimicrobial exposure, microorganisms have developed a vast array of antimicrobial resistance mechanisms, including the expression of hydrolytic enzymes, activation of efflux pump systems, and the alteration of cell wall permeability (Ref. 23). Many antimicrobial resistance genes are found on plasmids, which not only play an integral role in the horizontal transfer of resistance between organisms, but can also stack multiple resistance genes together on a single mobile element (Ref. 24). As a result, many of today's hospital-acquired infections involve bacteria that are resistant to multiple classes of antimicrobials, which may include both medically important antimicrobials along with other broad-spectrum antimicrobials (e.g., metals, biguanides, quaternary ammonium compounds) (Refs. 25 and 26).

Although all antimicrobial resistance is important, additional consideration is needed based on the level of importance a particular antimicrobial plays in human medicine and the availability of other therapeutic options to treat or mitigate specific infections (Refs. 6, 27-29).

While medically important antimicrobials (e.g., antibiotics) are the focal point of antimicrobial stewardship practices and resistance classification efforts, there are other antimicrobials that are routinely utilized in healthcare, such as antiseptics (which inhibit or kill microorganisms in or on living tissue, such as hand washes) and disinfectants (which inhibit or kill microorganisms on inanimate objects or surfaces) (Ref. 30).

Historically, wound dressings and liquid wound washes have utilized a wide range of antimicrobials as preservatives or protectants, each with a varying degree of AMR information detailed in the literature. When evaluating the level of AMR concern associated with antimicrobials used as preservatives or protectants in wound dressings and liquid wound washes, the probable benefit of the wound dressing and liquid wound wash should outweigh the probable risk of contributing to the development and spread of resistance, and, particularly, resistance to medically important antimicrobials. As such, FDA is proposing a risk-based approach for assessing the level of AMR concern (high, medium, or low) associated with wound dressings and liquid wound washes containing antimicrobials, as described in Section III.B Terminology.

Based on feedback from the 2016 Panel, a high level of AMR concern is associated with the use of medically important antimicrobials (e.g., antibiotics), as this may present an unreasonable risk of illness or injury by directly contributing to the selection of organisms in the patient that are resistant to medically important antimicrobials, potentially further limiting a clinician's therapeutic options. Likewise, it is important to understand and evaluate the potential for an antimicrobial to indirectly select for organisms with medically important antimicrobial resistance mechanisms via coselection mechanisms, such as coresistance and cross-resistance.

As antimicrobial resistance is an evolving topic with emerging resistance mechanisms being routinely developed and discovered, this risk-based approach provides the flexibility needed to address changes in future antimicrobial utility and the expanding AMR landscape. Classifying these wound dressings and liquid wound washes will provide clarity and transparency regarding the regulatory requirements (e.g., general controls, special controls, or

premarket approval) necessary to provide a reasonable assurance of safety and effectiveness. As antimicrobial resistance remains a priority for FDA, such an effort will further enhance our ongoing activities related to slowing the development of AMR to help ensure safe and effective use of antimicrobials in wound dressings and liquid wound washes intended for human use.

C. FDA's Current Regulatory Framework

The FD&C Act (21 U.S.C. 301 et seq.), as amended by the Medical Device Amendments of 1976 (1976 amendments) (Pub. L. 94-295), established a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the FD&C Act (21 U.S.C. 360c) established three classes of devices, reflecting the regulatory controls needed to provide reasonable assurance of their safety and effectiveness: class I (general controls), class II (general controls and special controls), and class III (premarket approval and general controls).

Section 513(a)(1) of the FD&C Act defines the three classes of devices. Class I devices are those devices for which the general controls of the FD&C Act (controls authorized by or under sections 501, 502, 510, 516, 518, 519, or 520 of the FD&C Act (21 U.S.C. 351, 352, 360, 360f, 360h, 360i, or 360j) or any combination of such sections) are sufficient to provide reasonable assurance of safety and effectiveness, or those devices for which insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of safety and effectiveness or to establish special controls to provide such assurance, but because the devices are not purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, and do not present a potential unreasonable risk of illness or injury, are to be regulated by general controls (section 513(a)(1)(A) of the FD&C Act).

Class II devices are those devices for which general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness, but for which there is sufficient information to establish special controls to provide such assurance, including the promulgation of performance standards, postmarket surveillance, patient registries, development

and dissemination of guidelines (including guidelines for the submission of clinical data in premarket notification submissions in accordance with section 510(k)), recommendations, and other appropriate actions as the Secretary deems necessary to provide such assurance (section 513(a)(1)(B) of the FD&C Act).

Class III devices are those devices for which insufficient information exists to determine that general controls (controls authorized by or under sections 501, 502, 510, 516, 518, 519, or 520 of the FD&C Act or any combination of such sections) and special controls would provide a reasonable assurance of safety and effectiveness, and are purported or represented for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or present a potential unreasonable risk of illness or injury (section 513(a)(1)(C) of the FD&C Act).

Under section 513(d) of the FD&C Act, FDA refers to devices that were in commercial distribution before the 1976 amendments as "preamendments devices." FDA classifies these devices after the Agency: (1) receives a recommendation from a device classification panel (an FDA advisory committee); (2) publishes the panel's recommendation for comment, along with a proposed regulation classifying the device; and (3) publishes a final regulation classifying the device (section 513(d)(1) of the FD&C Act). FDA has classified most preamendments devices under these procedures.

A person may market a preamendments device that has been classified into class III through premarket notification procedures without submission of a PMA until FDA issues a final regulation order under section 515(b) of the FD&C Act (21 U.S.C. 360e(b)) requiring premarket approval. FDA is also proposing, by proposed order published elsewhere in this issue of the *Federal Register*, to require the filing of PMAs for such devices.

After the enactment of the 1976 amendments, FDA undertook to identify and classify all preamendments devices in accordance with section 513(d) of the FD&C Act. As part of this effort, FDA has completed the classification process to classify four types of wound dressings, as

class I medical devices: (1) nonresorbable gauze/sponge for external use at § 878.4014; (2) hydrophilic wound dressing at § 878.4018; (3) occlusive wound dressing at § 878.4020; and (4) hydrogel wound dressing and burn dressing at § 878.4022. However, wound dressings that contain antimicrobials and/or other chemicals were not included in these prior actions and have not been separately classified to date.

D. History of This Rulemaking

As described previously, certain solid wound dressings; wound dressings formulated as a gel, cream, or ointment; and liquid wound washes containing antimicrobials and/or other chemicals are unclassified, preamendments devices. These devices have been subject to premarket review through a 510(k) submission and have been cleared for marketing if FDA considers the device to be substantially equivalent to a legally marketed predicate in accordance with section 513(i) of the FD&C Act. Currently, there are more than 500 legally marketed unclassified, preamendments wound dressings and liquid wound washes containing antimicrobials and/or other chemicals which have been cleared through the 510(k) pathway that would be subject to this proposed classification regulation.

Consistent with the FD&C Act, FDA convened the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee and held multiple meetings regarding the classification of wound dressings on: (1) November 27, 1998 (Ref. 1); (2) August 25 and 26, 2005 (Ref. 2); and (3) September 20 and 21, 2016 (Ref. 3). From these meetings, and FDA's research and findings, the Agency understands that wound dressings and liquid wound washes containing medically important antimicrobials pose more AMR risk than other wound dressings and liquid wound washes. Elsewhere in this issue of the *Federal Register*, FDA is proposing to classify unclassified, preamendments wound dressings and liquid wound washes containing medically important antimicrobials into class III. FDA is proposing this classification as FDA believes that insufficient information exists to determine that general controls and special controls would provide reasonable assurance of the safety and effectiveness of these devices and

these devices present a potential unreasonable risk of illness or injury. The proposed rule would also establish the identification, classification, and regulatory controls for certain solid wound dressings; wound dressings formulated as a gel, cream, or ointment; and liquid wound washes that contain antimicrobials and/or other chemicals.

1. 1998 General and Plastic Surgery Devices Panel

On November 27, 1998, FDA convened the General and Plastic Surgery Devices Panel (the 1998 Panel) to discuss the classification of five wound dressing categories and the reclassification of topical oxygen chambers for extremities (Ref. 1). At the meeting, FDA presented the following five types of unclassified, preamendments wound dressings for the 1998 Panel's classification recommendations: (1) nonresorbable gauze/sponges for external use; (2) hydrophilic wound dressings; (3) occlusive wound dressings, (4) hydrogel wound dressings; and (5) porcine wound dressings. FDA requested the 1998 Panel consider the proposed classifications for each of these wound dressings, including the product description and intended uses that should be included in the classification regulation for each dressing. FDA also requested the 1998 Panel discuss the risks to health for each dressing. FDA asked the 1998 Panel, as part of their deliberations, to consider the potential risk of viral transmission posed by porcine wound dressings.

The 1998 Panel unanimously concurred with a recommendation that all five identified wound dressings be classified in class I. The 1998 Panel also recommended that four of the five dressings: (1) nonresorbable gauze/sponges for external use; (2) hydrophilic wound dressings; (3) occlusive wound dressings; and (4) hydrogel wound dressings, be classified as exempt from premarket notification requirements. Subsequently, FDA classified these four dressing types under §§ 878.4014, 878.4018, 878.4020, and 878.4022, respectively (Ref. 4). Therefore, since these four dressings were previously classified, they are outside the scope of this proposed rule and will not be discussed further in this proposed rule. The fifth dressing type, porcine wound dressings, remained unclassified following the 1998 Panel meeting.

Although the 1998 Panel recommended that porcine wound dressings should be class I, the 1998 Panel believed that porcine wound dressings should not be exempt from premarket notification requirements due to concerns of potential viral contaminants and infectious diseases. Since FDA believes the risks of porcine wound dressings identified at the 1998 Panel meeting are also relevant to the wound dressings composed of animal-derived materials described in this proposed rule, a brief summary of the 1998 Panel discussion on porcine wound dressings is provided here. After considering the information provided by FDA, the open discussions during the 1998 Panel meeting, and the 1998 Panel members' experiences with these wound dressings at that time, the 1998 Panel provided reasons in support of its recommendation for classifying porcine wound dressings used to provide or support a moist wound environment, to cover a wound, to absorb exudate, and/or to minimize fluid loss into class I, not exempt from premarket notification requirements.

2. 2005 General and Plastic Surgery Devices Panel

On August 25 and 26, 2005, the General and Plastic Surgery Devices Panel (the 2005 Panel) met to provide advice and recommendations on the classification of five unclassified preamendments medical devices: (1) bone wax; (2) medical maggots; (3) medicinal leeches; (4) tissues expanders; and (5) wound dressings containing antimicrobials and/or other chemicals; however, for the purposes of this proposed rule, only the 2005 Panel's recommendations regarding wound dressings containing antimicrobials and/or other chemicals will be discussed (Ref. 2). At the 2005 Panel meeting, FDA proposed to describe the intended uses for these wound dressings containing antimicrobials and/or other chemicals, whether sterile or nonsterile, as being used to cover a wound, to absorb exudate, to provide or support a moist environment within the dressing, and to control bleeding or fluid loss. These wound dressings consist of nonabsorbable materials and contain added antimicrobials and/or other chemicals.

The 2005 Panel unanimously concurred to recommend that FDA classify wound dressings containing antimicrobials and/or other chemicals as class II medical devices requiring a

510(k) submission, subject to special controls. Some of the major risks identified by the 2005 Panel included the possibility that the antimicrobials and/or other chemicals could contribute to antimicrobial resistance, could sensitize the skin, interfere with wound healing, or result in selective colonization. But the 2005 Panel agreed with FDA that there is sufficient information to establish special controls that, together with general controls, would mitigate the risks to health and provide a reasonable assurance of safety and effectiveness for these products.

3. 2016 General and Plastic Surgery Devices Panel

The most recent Panel, held on September 20 and 21, 2016 (the 2016 Panel), met for the purposes of obtaining recommendations about the classification of products, including: (1) solid wound dressings; (2) wound dressings formulated as a gel, cream, or ointment; and (3) liquid wound washes. FDA held the 2016 Panel to obtain input on the benefits and risks of wound dressings and liquid wound washes that contain antimicrobials and/or other chemicals, as well as on the clinical relevance of certain indications. The 2016 Panel was asked to recommend to FDA whether such wound dressings and liquid wound washes that contain antimicrobials and/or other chemicals should be classified into class III (subject to PMA and general controls), class II (subject to general and special controls), or class I (subject only to general controls). The 2016 Panel was also asked to discuss the types of evidence (including clinical evidence) that would be helpful to support certain indications, as well as the appropriate controls necessary to mitigate the risks to health and assure the safety and effectiveness of these types of wound dressings and liquid wound washes.

For each type of wound dressing and liquid wound wash, FDA presented the proposed risks to health and proposed mitigation measures. FDA identified risks to health applicable to wound dressings and liquid wound washes, including adverse tissue reaction, delayed wound healing, incompatibilities with other therapies, increased risk of AMR, infection, microbial growth, and product degradation. Further, FDA identified that additional risks to health applicable to solid wound dressings included loss of barrier function and retention of dressing

material in the wound. FDA also identified that an additional risk applicable to liquid wound washes was the inability to remove wound debris. Following the 2016 Panel meeting, an additional risk to health was identified based on emerging reports in the literature (Refs. 31-37) regarding the understood role that our skin microbiota plays in the wound healing cascade. As such, antimicrobials that leach from wound dressings may inadvertently negatively impact the patient's skin microbiota in the periwound area resulting in impaired wound healing.

FDA presented information on the proposed mitigation measures for the risks to health of these wound dressings and liquid wound washes, which included biocompatibility, in vivo evaluation, clinical evaluation of dressings for specific intended uses and indications for use, labeling, evaluation and identification of any probable risk and mechanisms for AMR, sterilization and shelf-life validation, preservative effectiveness testing, and antimicrobial effectiveness testing. In addition to these identified mitigation measures, FDA proposed that the risk of loss of barrier function associated with solid wound dressings could be mitigated through microbial barrier effectiveness testing and water loss/moisture barrier effectiveness testing. Similarly, FDA proposed that the risk of inability to remove wound debris and foreign materials associated with liquid wound washes could be mitigated through appropriate bench performance testing. Regarding the understood risk that antimicrobials may inadvertently negatively impact the skin microbiota in the periwound area and impair wound healing, FDA proposes that this risk may be mitigated through antimicrobial characterization, performance testing, and labeling.

Regarding the benefit and risk assessments, the 2016 Panel noted that it is important to consider the heterogeneity in wound types when evaluating whether labeling claims represent clinically meaningful benefit to patients. For example, a labeling claim specifying use for a specific amount of time may be highly beneficial for dressings intended to be placed over a central venous catheter, but may not be as beneficial for burn wounds. The 2016 Panel also noted that when assessing the benefit-risk profile of a product, higher risk may be tolerated when

known benefit is high, whereas lower risk should be tolerated when known benefit is low or not established.

Regarding factors to consider when more than one antimicrobial is included in a single product, the 2016 Panel stated that it would be important to evaluate whether use of multiple antimicrobials in a single product would produce antagonistic, synergistic, or additive effects with respect to reducing bioburden and/or promoting AMR. The 2016 Panel noted that it is currently not well understood how the inclusion of more than one antimicrobial would impact the likelihood of developing AMR. When certain antimicrobials are used together, there is surveillance data that shows that the risk of selecting for resistance is higher. However, the 2016 Panel noted that sufficient surveillance data does not exist for many other groupings of antimicrobials.

For solid wound dressings, a majority of the 2016 Panel members recommended that these products be classified into class II, subject to special controls, with the exception of certain solid wound dressings containing antimicrobials, such as antibiotics (with similar consideration to antimicrobial agents that may select for resistance in indirect ways). For these exceptions, several members of the 2016 Panel recommended that these wound dressings be classified into class III, with one Panel member noting that "antibiotics should be held to an extremely high set of standards to prove value because of the risk of [antimicrobial] resistance]". Further, the 2016 Panel meeting included discussion to note that special controls, such as testing in an animal model, could not be used to evaluate and/or mitigate the risk of AMR, supporting the assertion of several Panel members that solid wound dressings containing antibiotics should be classified as class III devices. As such, some of the 2016 Panel members recommended that the AMR risk posed by certain antimicrobials, such as antibiotics, could be mitigated through the increased controls of the PMA regulatory pathway that would be applied to these wound dressings as class III devices.

Several of the 2016 Panel members stated that additional risks associated with solid wound dressings containing antimicrobials may include leaching and systemic absorption of the antimicrobials, delayed wound healing, retention of dressing material in the wound, and loss of barrier function. Regarding mitigation of risks, some 2016 Panel members stated that bench testing could be a potential mitigation measure for the risk of retention of dressing material in the wound. One Panel member added that labeling would be an additional mitigation measure for loss of barrier function since barrier function would be dependent on proper application of the wound dressing. The risk of leaching and systemic adsorption of antimicrobials and/or other chemicals is also covered in adverse tissue reaction and toxicity.

For wound dressings formulated as a gel, cream, or ointment, a majority of the 2016 Panel members recommended that these products be classified into class II, subject to special controls, with the exception of certain wound dressings formulated as a gel, cream, or ointment containing antimicrobials, such as antibiotics (with similar consideration to antimicrobial agents that may select for resistance in indirect ways), for which some members of the 2016 Panel recommended class III. Several of the 2016 Panel members referenced the prior discussion on solid wound dressings, wherein they recommended that classification should be stratified by the risk of the ingredients within the dressing. The reasons certain wound dressings formulated as a gel, cream, or ointment should be classified as class III devices, based on the inclusion of certain antimicrobials, such as antibiotics, aligned with the rationale discussed during the deliberations on solid wound dressings. Also, some 2016 Panel members stated that cumulative residual material in the wound could present an additional potential risk that could be mitigated by specific labeling requirements. The risks of systemic absorption and topical toxicity were also concerning to the 2016 Panel. Some 2016 Panel members questioned whether antimicrobials should be included in a gel, cream, or ointment at all when there may be physical or non-antimicrobial means to reduce bioburden in the product.

For liquid wound washes, a majority of the 2016 Panel recommended that these products be classified into class I or class II, subject to special controls, depending on the toxicity of the product, with the exception of certain liquid wound washes containing antimicrobials, such as antibiotics (with similar consideration to antimicrobial agents that may select for resistance in indirect ways), for which some members of the 2016 Panel recommended class III. To support this opinion on classifying liquid wound washes containing antimicrobials, such as antibiotics, as class III devices, several of the 2016 Panel members referenced the prior discussion regarding solid wound dressings, where it was noted that special controls could not mitigate the risks posed by these products and that classification of these products should be stratified based on risk of AMR. Some of the 2016 Panel members felt that the identified risk of "inability to remove wound debris and foreign materials" would be better refined as "inadequate or possible incomplete removal of wound debris and foreign materials." The 2016 Panel discussed the clinical value of debridement and irrigation and questioned the value of added agents. There was agreement that agents in the liquid wound wash would affect the wound directly, and there was skepticism regarding whether these products should contain antimicrobials at all.

IV. Legal Authority

The Agency is proposing this classification under the authority of section 301 of the FD&C Act (21 U.S.C. 301). Specifically, the relevant authority related to the proposed classification includes sections 513(a) through (d) of the FD&C Act regarding device classes, classification, and panels; section 515 of the FD&C Act regarding PMAs; and section 701(a) of the FD&C Act (21 U.S.C. 371(a)).

V. Description of the Proposed Rule

A. Scope/Applicability

We are proposing to amend subpart E of 21 CFR part 878 by adding § 878.4016 to classify solid wound dressings containing antimicrobials and/or other chemicals used to cover and protect a wound, to absorb exudate, and to maintain appropriate moisture balance within the

wound; § 878.4017 to classify wound dressings formulated as a gel, cream, or ointment containing antimicrobials and/or other chemicals used to maintain appropriate moisture balance within the wound; and § 878.4019 to classify liquid wound washes used to mechanically irrigate and physically remove debris from external wounds and to moisten solid wound dressings in accordance with section 513(d) of the FD&C Act. Please note that wound dressings and liquid wound washes generally achieve the maintenance of a moist wound environment through nonchemical action (e.g., by acting as a barrier).

Wound dressings and liquid wound washes that achieve the maintenance of a moist wound environment through chemical action would be outside the scope of this proposed rule and may be drugs or combination products. For information on the classification of products as drugs, devices or biological products, see the guidance "Classification of Products as Drugs and Devices and Additional Product Classification Issues" (Ref. 38). Examples of antimicrobials and categories and examples of other chemicals are identified in tables 2 and 3, respectively. This proposed classification rule applies to certain wound dressings and liquid wound washes currently regulated under the product codes FRO, GER, MGP, MGQ, and EFQ. The proposed rule only applies to wound dressings and liquid wound washes that are for use on external cutaneous (skin) wounds.

The following categories of wound dressings are outside the scope of this proposed rule and classification action because they are currently regulated either as a distinct category within the product code FRO or under a different product code,[19] as identified:

- Wound dressings composed of animal-derived materials without the presence of antimicrobials and/or other chemicals, as they are currently regulated under product code KGN.

[19] More detail about the medical device names and associated information for the product codes listed here is available in the Product Code Classification Database, available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm.

- Wound dressings with or without an added antimicrobial or biologic (e.g., thrombin) that is used to provide hemostasis through accelerated blood clotting when combined with manual compression, as they were discussed in October 2022 at a Classification Panel.[20, 21]
- Absorbable synthetic wound dressings without antimicrobials that are intended to degrade and be resorbed into the wound.[22]
- Catheter securement dressings containing antimicrobials that are intended for reduction or prevention of infection (e.g., central line-associated bloodstream infection).[23, 24]
- Dressings with topical analgesics, such as lidocaine or benzocaine.[25]
- Dressings with hydrocortisone.[26]
- Wound dressings used on mucosa, such as for oral uses or use in the gastrointestinal tract.

The following categories of wound dressings are outside the scope of this proposed rule and classification action because FDA has previously classified them:

- Nonresorbable gauze/sponge for external use at § 878.4014 (Product Codes: MAC, OVR, LZM, NAB, OHO, PKD, PXY, PYJ, PYK, PYL)
- Hydrophilic wound dressing at § 878.4018 (Product Codes: KOZ, MGO, NAC)
- Occlusive wound dressing at § 878.4020 (Product Code: NAD)
- Hydrogel wound dressing and burn dressing at § 878.4022 (Product Codes: NAE, OJJ, PXQ);

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[20] 87 FR 60691, October 6, 2022. Available at https://www.govinfo.gov/content/pkg/FR-2022-10-06/pdf/2022-21746.pdf. FDA will add a link to the meeting materials once they are publicly available.
[21] These dressings are currently regulated under product code FRO, but FDA's intent will be to assign a new product code for these wound dressings as they are out of the scope of this proposed rule and proposed classification action.
[22] Id.
[23] The majority of the catheter securement dressings with antimicrobials are in scope for this proposed rule and proposed classification action. Catheter securement dressings containing antimicrobials that are intended for reduction or prevention of infection are outside the scope of this proposed rule.
[24] These dressings are currently regulated under product code FRO, but FDA's intent will be to assign a new product code for these wound dressings, as they are out of scope of this proposed rule and proposed classification action.
[25] Id.
[26] Id.

- Wound dressing with poly (diallyl dimethyl ammonium chloride) (pDADMAC) additive at § 878.4015 (Product Code: NYS).

(Refs. 39-40)

B. Device Description

1. Solid Wound Dressings Containing Antimicrobials and/or Other Chemicals

Solid wound dressings containing antimicrobials and/or other chemicals are used to cover and protect a wound, to absorb exudate, and to maintain appropriate moisture balance within the wound (see intended uses in section V.B). The antimicrobials (see table 2) contained in solid wound dressings are used as a protectant to prevent or reduce contamination or deterioration of the dressing while in contact with the wound. A solid wound dressing may contain one or more of the antimicrobials (see table 2) and/or other chemicals (see table 3). Such a wound dressing may also contain animal-derived materials (e.g., collagen, gelatin, decellularized extracellular matrix).

The dressing materials are resorbable or nonresorbable, synthetic or naturally derived materials (including animal-derived materials), which are provided sterile in a form able to hold structural integrity permanently or temporarily. Solid wound dressings containing antimicrobials and/or other chemicals may be in the form of a woven or nonwoven fabric pad, foam, or as a cross-linked hydrogel that has sufficient structural integrity to hold a physical form, such as a scaffold or matrix. Some wound dressings are multilayered, with each layer made of a different solid form, such as a four-layered dressing with a woven layer, foam layer, hydrocolloid layer, and occlusive adhesive backing layer. The types of materials used in these wound dressings generally include polyester, cellulose, polyurethane, nylon, poly(vinyl alcohol), alginate, cross-linked collagen, poly(ethylene glycol), and poly(lactic-co-glycolic acid).

2. Wound Dressings Formulated as a Gel, Cream, or Ointment Containing Antimicrobials and/or Other Chemicals

A wound dressing formulated as a gel, cream, or ointment containing antimicrobials and/or other chemicals is used to maintain appropriate moisture balance within the wound (see intended uses in section V.B). The antimicrobials contained in such wound dressings are used for preservative purposes to maintain shelf life for a nonsterile wound dressing or a multiple-use wound dressing for single patient use only (see table 2). A wound dressing formulated as a gel, cream, or ointment may contain one or more of the antimicrobials (see table 2) and/or other chemicals (see table 3). Such a wound dressing may also contain animal-derived materials.

The wound dressing materials are synthetic or naturally derived materials (including animal-derived materials), which are provided in an amorphous form. Wound dressings formulated as a gel, cream, or ointment containing antimicrobials and/or other chemicals are amorphous and can have high water content with thickening agents or consist of an oil-water emulsion. These products are generally packaged in tubes or containers that can be for single use only or labeled for multiple use for single patient use only after the package has been opened. While some wound dressings are terminally sterilized and labeled for single use, many other wound dressings cannot be terminally sterilized given the sensitivity of the materials to sterilization methods, or they may require a preservative for multiple-use wound dressings for single patient use only.

3. Liquid Wound Washes

A liquid wound wash is a water-based solution used to mechanically irrigate and physically remove debris from external wounds. It is also used to moisten solid wound dressings to maintain appropriate moisture balance within the dressing (see intended use(s) in section V.B). The antimicrobials contained in such liquid wound washes are used for preservative purposes to maintain shelf life for a nonsterile liquid wound wash or a multiple-use liquid wound wash for single patient use only (see table 2). Some liquid wound washes are terminally sterilized and labeled for single use, or they may require a preservative for multiple-use liquid

wound washes for single patient use only. Liquid wound washes may contain one or more of the antimicrobials (see table 2) and/or other chemicals (see table 3).

Liquid wound washes are generally water- or saline-based liquid solutions. They are typically packaged in bottles with plain caps or pump sprays and may or may not be terminally sterilized. Such liquid wound washes may also contain animal-derived materials.

4. Proposed Intended Use(s)

Based on the collective recommendations from the 2005 and 2016 Panels, FDA's experience with these wound dressings and liquid wound washes, and other available information, FDA proposes the following intended uses for the three wound dressing and liquid wound wash types discussed in this proposed rule. Additionally, since the utilization of these wound dressings and liquid wound washes is not to treat an infection, FDA is proposing that the intended uses for these wound dressings and liquid wound washes remain the same whether the product is used for an infected or noninfected wound because the role of the antimicrobial is limited to acting within the dressing and not on the wound itself. The proposed uses are the following:

- *Solid Wound Dressings Containing Antimicrobials and/or Other Chemicals*: A solid wound dressing containing antimicrobials and/or other chemicals is used to cover and protect a wound, to absorb exudate, and to maintain appropriate moisture balance within the wound.
- *Wound Dressings formulated as a Gel, Cream, or Ointment Containing Antimicrobials and/or Other Chemicals*: A wound dressing formulated as a gel, cream, or ointment containing antimicrobials and/or other chemicals is used to maintain appropriate moisture balance within the wound.
- *Liquid Wound Washes*: A liquid wound wash is a water-based solution used to mechanically irrigate and physically remove debris from external wounds. It is also used

to moisten solid wound dressings to maintain appropriate moisture balance within the dressing.

Within those intended uses, antimicrobials may support the intended use through the following means:

- *Antimicrobial preservative*: An antimicrobial preservative is used in wound dressings formulated as a gel, cream, or ointment or liquid wound washes to maintain low bioburden while in its packaging during storage to improve its shelf life. An antimicrobial preservative use is not appropriate for a sterile, single-use product. Further, preservative effectiveness claims are within the scope of this proposed rule for the proposed classifications only when used for a specified period of use for multiple-use wound dressings and liquid wound washes for single patient only use.
- *Antimicrobial protectant*: An antimicrobial protectant, when added to a sterile, single-use solid wound dressing, is intended to support the use of the wound dressing by reducing degradation or biofouling of the dressing while in use. Antimicrobial protectant claims are within the scope of this proposed rule for the proposed classifications only when used for reducing microbial growth within the solid wound dressing for a specified maximum period of clinical use.

Prior to this proposed rulemaking, wound dressings and liquid wound washes containing antimicrobials intended for wound management were generally identified as combination products.[27] This was because the term "wound management" could be interpreted broadly, encompassing uses not only including to cover and protect a wound, to absorb exudate, and to maintain appropriate moisture balance, but also uses such as treatment of wounds/wound infection. As discussed in more detail below, for a product to be within the scope of this proposed rulemaking and benefit from the proposed classification action, FDA is proposing that

[27] See definition of combination product in 21 CFR 3.2(e).

the term "wound management" not be included in the product labeling and the product labeling be clarified to reflect the explicit uses described above (e.g., "to protect and cover a wound").

FDA has considered the intended use of these products in this category limited to the uses expressly discussed above (including to cover and protect a wound, to absorb exudate, to maintain appropriate moisture balance, to mechanically irrigate). However, with the inclusion of "wound management" and based on feedback during the 2016 Panel (Ref. 3), these limited intended uses were not clear to all users and, thus, created a broader objective intent. Within the scope of this proposed rule, FDA is making manufacturers aware that, for their products to be within the scope of this proposed rulemaking and benefit from the proposed classification action, manufacturers must clarify their labeling to not include "management" but instead explicitly include the relevant uses described above. Otherwise, the product could be subject to a different type of marketing authorization, depending on the product claims. In many cases, refinement of the indications will require revisions to the labeling.

FDA believes that, with such clarification of statements in the labeling and the indications, wound dressings and liquid wound washes in this category, including those with appropriate amounts of antimicrobial, should be regulated only as "devices" and not as combination products. This is because the antimicrobial, when included in a product that only covers and protects a wound, absorbs exudate, irrigates a wound, and/or maintains appropriate moisture balance would not achieve its primary intended purpose through chemical action within or on the body of man.[28]

Manufacturers who do not intend to update their products' labeling to clarify such claims (i.e., update to remove wound management and other misleading claims discussed below) would not be in compliance with the special controls when the rule is finalized. Hence, these

[28] See section 201(h) of the FD&C Act (21 U.S.C. 321(h))--for the definition of device. For guidance on how products are classified as devices, please see the guidance "Classification of Products as Drugs and Devices and Additional Product Classification Issues" (https://www.fda.gov/media/80384/download).

manufacturers' products could be subject to submission of their wound dressing or liquid wound wash to FDA for review via a different type of marketing authorization, depending on the product claims. For example, wound dressings containing antimicrobials that make certain wound management claims may be considered combination products or drugs and regulated as such.

FDA proposes that the following labeling claims are not appropriate for the wound dressings and liquid wound washes proposed for classification in this proposed rule as these claims may be unclear or misleading or indicate an objective intent outside of the intended uses discussed above. While some of these uses may have been previously reviewed in submissions for wound dressings and liquid wound washes within the scope of this rule, FDA is proposing to clarify, consistent with the recommendations of the 2005 and 2016 Panels and FDA's experience with these dressings and washes, that such uses are inappropriate for the wound dressings and liquid wound washes being proposed for classification through this rulemaking. These uses include the following:

- *Wound Management*: While the term has been widely used, it is not consistently used and is unclear from a clinical perspective. Based on the 2016 Panel discussion, the Panel members agreed that specific functions of wound dressings and liquid wound washes had clear benefits, including covering and protecting a wound, keeping the dressing moist, and washing or irrigating a wound. Although the term "wound management" was presented as a typical part of the indications and intended use of wound dressings and liquid wound washes, the 2016 Panel members acknowledged that there was not a consistent or frequent use of the term "wound management" in describing how the products are used. The 2016 Panel members questioned whether the wound dressings and liquid wound washes are intended to treat the wound or to achieve wound healing. Therefore, consistent with the 2016 Panel's feedback, this proposed rulemaking is clarifying that the term "wound management" be replaced with the specific functions of

the wound dressing and liquid wound washes (e.g., cover and protect the wound in the case of solid wound dressings).

- *Use of the word "may" (e.g., "may reduce the risk of infection")*: The word "may" is ambiguous and could mislead the end users when describing a specific use (e.g., "may reduce the risk of infection"); instead, intended uses, indications, and claims should be clearly stated and supported by appropriate data. This is supported by the fact that the 2016 Panel discussed whether the term "may reduce the risk of infection" represented a clinically meaningful benefit to the patient, and noted that such a claim does not appear to be meaningful and is likely confusing to patients.
- *Treatment of or cure for wounds*: This use is for wound healing through active interaction with the wound. Such a use falls within the scope of product codes MGR or MDD, which are regulated as a postamendments class III device, subject to PMA.
- *Deliver antimicrobials to the wound*: Such use suggests an intent for the treatment or prevention of infection that generally would be achieved through chemical action within or on the wound and may not fall under CDRH's jurisdiction. For the purposes of this classification action, the role of the antimicrobial(s) is limited to acting within the wound dressing or liquid wound wash as either a preservative or a protectant of the product.
- *Antimicrobial preservative claims for a sterile, single-use product*: Use of a preservative in this context is limited only to nonsterile, single-use or multiple-use wound dressings for single patient use only.[29]

FDA encourages sponsors to consider the following in support of their proposed intended use(s) when demonstrating they fall within the scope of this proposed rule and classification action.

[29] In rare cases, antimicrobials can be included as a process control to reduce bioburden during manufacturing, and this should be supported with proper justification and discussed with the review team. No performance claims should be made regarding the use of antimicrobials as manufacturing process controls.

- Preservative effectiveness claims for wound dressings formulated as a gel, cream, or ointment, and liquid wound washes should be defined for a specified period of shelf storage, and supported by appropriate in vitro testing as outlined in USP <51> "Antimicrobial Effectiveness Testing," including following specific recommendations concerning test organisms and acceptance criteria.
- Antimicrobial effectiveness claims for solid wound dressings should describe the general level of effectiveness (i.e., reduced microbial growth within the solid dressing or barrier to microbial penetration through a solid dressing over a specified period of use) and should be supported by in vitro test results from a broad selection of representative clinically relevant microbial species, as described in the proposed performance testing special controls identified in section V.B. However, due to the genetic diversity within the different microbial species, effectiveness claims on product labeling should only describe the general level of effectiveness, without listing specific test organisms, species, or strains (including drug resistant strains such as Methicillin-resistant *Staphylococcus aureus*).
- Antimicrobial effectiveness claims for solid wound dressings should clearly distinguish the types of data used to support the claim; for example, whether the claim is based on results from in vitro testing, in vivo testing, or supporting clinical data. For claims that are solely supported by in vitro testing, the submission and product labeling should clearly state that the claims are solely based on in vitro testing and that clinical studies were not conducted or that the clinical benefit has not been evaluated.
- Antimicrobial and preservative effectiveness claims for all wound dressings containing antimicrobials should not state or imply that these products have an antimicrobial impact on organisms in the wound environment since claims regarding effectiveness against wound microorganisms and biofilms would be outside the scope of this proposed rule.

C. Risks to Health and Public Health Benefits

In evaluating the risks to health associated with the use of wound dressings and liquid wound washes, FDA considered information from the 1998 Panel, the 2005 Panel, and the 2016 Panel regarding the classification of wound dressings and liquid wound washes; the adverse event reports for these wound dressings and liquid wound washes in FDA's Manufacturer and User Facility Device Experience database examined through July 2022; and the published scientific literature, which is discussed in FDA's executive summary for the 2016 Panel meeting (Ref. 3).

FDA also considered scientific literature published since the 2016 Panel meeting. A contemporary literature search was conducted in September 2022 and identified eight articles (Refs. 41-48) published since June 2016 that are relevant to the safety and effectiveness of wound dressings and liquid wound washes containing antimicrobials. In the review of these references, the information from the contemporary literature analysis is consistent with the findings of the prior literature analysis presented at the 2016 Panel meeting.

FDA also reviewed recalls reported under product code FRO from 2003 to July 2022.[30] There were no recalls for solid wound dressings; wound dressings formulated as a gel, cream, or ointment; or liquid wound washes containing medically important antimicrobials acting as either protectants or preservatives during this same timeframe. Out of the 29 recalls identified for wound dressings and liquid wound washes containing medium or low level of AMR concern and/or other chemicals, there was 1 class I recall, 23 class II recalls, and 5 class III recalls. The reason for the one class I recall was potential microbial contamination of the product. Reasons for class II and class III recalls include erroneous device labeling, devices not meeting stability specifications, and potential sterility breach of the product. Based on this information, FDA believes the risks to health associated with the use of these wound dressings and liquid wound washes are those discussed below.

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[30] Only the product code FRO was queried for the recall analysis, as the majority of the products in scope for this proposed rule fall within FRO. The types of recalls reported within FRO are expected to be representative of all products in scope for this proposed rule.

Based on this information, FDA has identified the following risks to health to the different categories of wound dressings and liquid wound washes which are within the scope of this proposed rule and classification action:

- *Solid Wound Dressings*: adverse tissue reaction, immunological reaction, transmission of pathogens and parasites, toxicity, delayed wound healing, incompatibilities with other therapies, contribution to the spread of AMR, infection, microbial growth within the product, product degradation during stated shelf storage, loss of barrier function, retention of dressing material in wound, and negatively impacting the skin microbiota in the periwound area resulting in impaired wound healing.
- *Wound Dressings Formulated as a Gel, Cream, or Ointment*: adverse tissue reaction, immunological reaction, transmission of pathogens and parasites, toxicity, delayed wound healing, incompatibilities with other therapies, contribution to the spread of AMR, infection, microbial growth within the product, product degradation during stated shelf storage, and negatively impacting the skin microbiota in the periwound area resulting in impaired wound healing.
- *Liquid Wound Washes*: adverse tissue reaction, immunological reaction, transmission of pathogens and parasites, toxicity, delayed wound healing, incompatibilities with other therapies, contribution to the spread of AMR, infection, microbial growth within the product, product degradation during stated shelf storage, inability to remove wound debris and foreign materials, and negatively impacting the skin microbiota in the periwound area resulting in impaired wound healing.

Below is a brief description of each of the identified risks to health:

- *Adverse tissue reaction:* Erythema, irritation, inflammation of the wound or host tissue, immune response, and hemolysis can occur as a result of an unwanted tissue response associated with the materials or leachables/extractables in wound dressings and liquid wound washes.

- *Immunological reaction*: This can result from a device derived from a new animal source or protein denaturation/modification due to the manufacturing conditions.
- *Transmission of pathogens and parasites* (e.g., bacteria, mycoplasma, fungi, viruses, and other transmissible spongiform encephalopathy agents): This can result from contaminated animal sources, feed, inadequate processing, and viral inactivation of the animal-derived materials.
- *Toxicity:* Local and/or systemic toxicity, tissue necrosis, reduced tissue viability, and genotoxicity can occur due to toxic antimicrobials or other chemicals in the wound dressings or liquid wound washes, which can result in adverse tissue effects, leading to toxicity. This also includes allergic reaction and sensitization, as individuals with known sensitivity to the materials in the wound dressings and liquid wound washes may experience allergic reactions, which may be severe depending on the degree of sensitivity.
- *Delayed wound healing:* Cytotoxicity resulting in dead or necrotic tissue can delay healing.
- *Incompatibilities with other therapies:* An undesirable (e.g., antagonistic) reaction could occur between the materials contained in/on the wound dressings or liquid wound washes and other therapies applied to the wound.
- *Contribution to the spread of AMR:* Use of antimicrobials in wound dressings and liquid wound washes can inadvertently select for and cultivate antimicrobial resistant organisms in patients and further limit a clinician's therapeutic options to treat infections.
- *Infection:* Unsafe methods of manufacturing processes, such as inadequate aseptic processing, inadequate packaging and/or product storage can result in contaminated product that may be a source of infection. This risk includes bacterial and fungal infections and superinfections which may result from the use of an antimicrobial-containing wound dressing or liquid wound wash that introduces contaminating

microorganisms to the wound or disrupts the natural balance of skin flora around the wound.

- *Microbial growth within the product:* This can occur from inadequate sterilization, preservative effectiveness failure, unsafe methods of manufacturing processes, inadequate packaging and/or product storage. This can lead to a change in product composition or characteristics (e.g., loss of tensile strength, change in pH) and may also result in infection or adverse tissue reaction.
- *Product degradation during stated shelf storage:* Inadequate packaging and/or inappropriate storage of wound dressings or liquid wound washes can result in product degradation during storage. Product degradation can also change the composition or characteristics of the product over time and lead to patient harm.
- *Retention of dressing material in wound:* This risk is generally applicable to solid wound dressings, which can occur due to a loss in solid dressing integrity or unintended degradation of solid wound dressings. It may also occur due to a healthcare provider inadvertently leaving material in the wound. This can lead to adverse tissue reaction, delay in wound healing, or infection.
- *Inability to remove wound debris and foreign materials:* Ineffective washing of the wound can occur. Debris and foreign material remaining in the wound can delay healing or lead to infection. This risk is applicable to the liquid wound washes containing antimicrobials and/or other chemicals.
- *Loss of barrier function:* This risk is applicable to solid wound dressings indicated as barriers to microbial penetration through the wound dressing (either via mechanical or antimicrobial properties). Loss of this barrier function can introduce microbial contamination from the environment into the wound and can lead to delay in wound healing or infection.

- *Impact to skin microbiota in the periwound area*: This risk is applicable to each category of antimicrobial-containing wound dressings. Inadvertent leaching of antimicrobials away from the dressing may negatively impact the skin microbiota in the periwound area by reducing the presence of beneficial commensal microorganisms that play a role in the wound healing cascade, resulting in impaired wound healing.

The purported benefits associated with the use of wound dressings and liquid wound washes that are proposed to be classified into either class III or II are discussed below.

In evaluating the benefits associated with the use of wound dressings and liquid wound washes containing antimicrobials and/or other chemicals, FDA considered information from the 1998 Panel, the 2005 Panel, and the 2016 Panel regarding the classification of wound dressings and liquid wound washes and the published scientific literature, including clinical guidelines for wound care, which is discussed in FDA's executive summary for the 2016 Panel meeting (Ref. 3). Based on this information, there appears to be a lack of clinical data to demonstrate a clear clinical benefit (e.g., improved clinical outcomes from the use of antimicrobial dressings over non-antimicrobial dressings for the prevention or treatment of local wound infections or to improve wound healing) regarding the use of wound dressings and liquid wound washes containing antimicrobials and/or other chemicals. It is generally understood from the literature review and discussion with the 2016 Panel members that the collection of such clinical data has been challenging, as a result of many factors (e.g., difficulties grouping patients with different wound types, lack of controls, unclear endpoints, other treatments including use of systemic antibacterial drugs, exclusion criteria, and identifying a sufficient number of patients to power these studies). Despite the lack of clear clinical data, several benefits to wound dressings and liquid wound washes containing antimicrobials and/or other chemicals have been identified, including the following:

- *Maintaining a moist wound healing environment:* Clinical guidelines note that a moist wound environment is ideal for wound healing. Wound dressings can provide this benefit

based on their ability to absorb and manage wound exudate levels. Wound dressings may include ingredients that aid in moisture management, for example, through acting as a humectant to manage moisture levels within the dressing or forming a barrier to moisture loss.

- *Providing effective barrier to environmental contaminants:* This benefit applies to solid wound dressings that utilize either a mechanical barrier (e.g., polyurethane film layer) or an antimicrobial barrier to eliminate the penetration of external microorganisms through the dressing and into the wound.
- *Reducing microbial growth within the dressing:* This benefit applies to solid wound dressings that utilize an antimicrobial to reduce microbial growth and colonization of dressings, which can reduce soiling and degradation of a dressing and extend the length of time a dressing may be applied before needing to be changed.
- *Extending the shelf life of nonsterile and/or multiuse wound dressings*: This benefit applies to wound dressings formulated as a gel, cream, or ointment and liquid wound washes that utilize an antimicrobial as a preservative to reduce microbial growth within the product during shelf storage. This helps keep dressings from prematurely degrading or becoming a source of cross-contamination.

Finally, it is noted that selection of certain wound dressings and liquid wound washes is based on wound bed characteristics, and due to their heterogenous nature, no single wound dressing or liquid wound wash is suitable for all types of wounds. As such, the robust number and diversity of wound dressings and liquid wound washes currently on the market provides an overall benefit of choice for healthcare professionals and other end users to select wound dressings and liquid wound washes that are tailored to the wound characteristics of a particular patient.

D. Proposed Classification and FDA's Findings

1. Level of AMR Concern and Medically Important Antimicrobials

FDA is proposing the following risk-based paradigm for evaluating the level of AMR concern (high, medium, or low) associated with wound dressings and liquid wound washes containing antimicrobials discussed in this proposed classification rule. The proposed paradigm is based on a detailed characterization of the antimicrobials contained in wound dressings and liquid wound washes cleared by FDA under product codes FRO, GER, MGP, MGQ, and EFQ, and by relying on FDA's experience in this area, literature review, the 2005 and 2016 Panels' recommendations, and other available information.

To evaluate the level of AMR concern and the proposed risk-based paradigm, a literature review was conducted to identify the following attributes: (1) current applications of the antimicrobial, (2) known resistance mechanisms, (3) if any of the resistance genes are plasmid-mediated, (4) evidence of potential for coselection of medically important antimicrobial resistance via mechanisms such as coresistance or cross-resistance, and (5) known resistant microbial species. FDA is proposing to categorize certain wound dressings and liquid wound washes as either having a high, medium, or low level of AMR concern, which then corresponds with the proposed classification of the wound dressings and liquid wound washes containing antimicrobials (as either being in class III or class II, based on the criteria in section 513(a)(1) of the FD&C Act).

2. Proposed Classification of Solid Wound Dressings Containing Antimicrobials and/or Other Chemicals (Proposed § 878.4016)

Based on FDA's experience with certain wound dressings, the collective 2005 and 2016 Panels' recommendations, and other available information, FDA is proposing to classify solid wound dressings containing medically important antimicrobials used as protectants (see table 2) into class III when intended to be used to cover and protect a wound, to absorb exudate, and to maintain appropriate moisture balance within the wound (proposed § 878.4016(b)(1)). These wound dressings may additionally contain other chemicals (see table 3). FDA is proposing this classification as FDA believes that insufficient information exists to determine that general

controls and special controls would provide reasonable assurance of safety and effectiveness for such wound dressings and these wound dressings present a potential unreasonable risk of illness or injury. FDA is also proposing, by proposed order published elsewhere in this issue of the *Federal Register*, to require the filing of a PMA if these wound dressings are classified into class III, which will only be finalized if FDA classifies such wound dressings as class III.

In proposed § 878.4016(b)(2), FDA is proposing to classify solid wound dressings containing antimicrobial(s) used as protectants with a medium or low level of AMR concern (see table 2) and/or other chemicals (see table 3) into class II (special controls). FDA is proposing this action based on the determination that general controls alone are not sufficient to provide reasonable assurance of the safety and effectiveness of these wound dressings, and there is sufficient information to establish special controls to provide such assurance.

The special controls proposed in § 878.4016(b)(2)(i) through (vii) for these proposed class II wound dressings include performance testing and descriptive information, antimicrobial characterization and performance testing, AMR risk assessment, biocompatibility evaluation, risk management assessment for animal-derived materials and/or botanical extracts, labeling, shelf life validation, and sterilization validation.

3. Proposed Classification for Wound Dressings formulated as a Gel, Cream, or Ointment Containing Antimicrobials and/or Other Chemicals (Proposed § 878.4017)

Based on FDA's experience with certain wound dressings, the collective 2005 and 2016 Panels' recommendations, and other available information, FDA is proposing to classify wound dressings formulated as a gel, cream, or ointment containing medically important antimicrobials used as preservatives (see table 2), into class III when intended to maintain appropriate moisture balance within the wound (proposed § 878.4017(b)(1)). These wound dressings may additionally contain other chemicals (see table 3). FDA is proposing this classification as FDA believes that insufficient information exists to determine that general controls and special controls would provide reasonable assurance of the safety and effectiveness for such wound dressings and these

wound dressings present a potential unreasonable risk of illness or injury. FDA is also proposing, by proposed order published elsewhere in this issue of the *Federal Register*, to require the filing of a PMA if these wound dressings are classified into class III, which will only be finalized if FDA classifies such wound dressings as class III.

In proposed § 878.4017(b)(2), FDA is proposing to classify wound dressings formulated as a gel, cream, or ointment containing antimicrobials used as preservatives with a medium or low level of AMR concern (see table 2) and/or other chemicals (see table 3) into class II (special controls). FDA is proposing this action based on the determination that general controls alone are not sufficient to provide reasonable assurance of the safety and effectiveness of these wound dressings, and there is sufficient information to establish special controls to provide such assurance.

The special controls proposed in § 878.4017(b)(2)(i) through (vii) include performance testing and descriptive information, antimicrobial characterization and preservative effectiveness testing, AMR risk assessment, biocompatibility evaluation, risk management assessment for animal-derived materials and/or botanical extracts, labeling, shelf-life validation, and sterilization validation.

4. Proposed Classification for Liquid Wound Washes (Proposed § 878.4019)

Based on FDA's experience with certain wound dressings and liquid wound washes, the collective 2005 and 2016 Panels' recommendations, and other available information, FDA is proposing to classify liquid wound washes containing medically important antimicrobials used as preservatives (see table 2) into class III when intended to irrigate the wound and to moisten solid wound dressings to maintain appropriate moisture balance within the dressing (proposed § 878.4019(b)(1)). These liquid wound washes may additionally contain other chemicals (see table 3). FDA is proposing this classification as it believes that insufficient information exists to determine that general controls and special controls would provide reasonable assurance of safety and effectiveness for such liquid wound washes and these washes present a potential

unreasonable risk of illness or injury. FDA is also proposing, by proposed order published elsewhere in this issue of the *Federal Register*, to require the filing of a PMA if these liquid wound washes are classified into class III, which will only be finalized if FDA classifies such liquid wound washes as class III.

In proposed § 878.4018(b)(2), FDA is proposing to classify liquid wound washes containing antimicrobials used as preservatives with a medium or low level of AMR concern (see table 2) or other chemicals (see table 3) into class II (special controls). FDA is proposing this action based on the determination that general controls alone are not sufficient to provide reasonable assurance of the safety and effectiveness of these liquid wound washes and there is sufficient information to establish special controls to provide such assurance.

The special controls proposed in § 878.4018(b)(2)(i) through (vii) include performance testing and descriptive information, antimicrobial characterization and preservative effectiveness testing, AMR risk assessment, biocompatibility evaluation, risk management assessment for animal-derived materials and/or botanical extracts, labeling, shelf-life validation, and sterilization validation.

In addition, if this proposed rule and classification is finalized, FDA plans to publish a notice in the *Federal Register* announcing its intent to exempt from the premarket notification requirements liquid wound washes containing water or 0.9 percent saline only, which do not contain antimicrobials, other chemicals, or animal-derived materials, subject to certain limitations. FDA believes that a 510(k) is not necessary to provide reasonable assurance of the safety and effectiveness of this wound wash type, in accordance with section 510(m) of the FD&C Act.

5. Proposed Special Controls

Based on the collective 2005 and 2016 Panels' recommendations, FDA's experience with these wound dressings and liquid wound washes, and other available information, FDA is proposing the special controls identified in this section for wound dressings and liquid wound

washes that are proposed to be classified into class II. FDA believes that these special controls, in addition to general controls, are necessary to provide a reasonable assurance of safety and effectiveness of the wound dressings and liquid wound washes containing antimicrobials used as either protectants or preservatives with a medium or low level of AMR concern (see table 2) and/or other chemicals (see table 3). Special controls were discussed at the 2016 Panel (Ref. 2, see section III.B of the Executive Summary). The 2016 Panel agreed that the special controls as presented would provide a reasonable assurance of safety and effectiveness for these wound dressings and liquid wound washes, emphasizing in discussions, among other things, the need for adequate labeling, specific use claims, and sufficient data to support labeling claims.

As noted in Section V.C Risks to Health and Public Health Benefits of this proposed rule, three risks (specifically, toxicity, transmission of pathogens and parasites, and immunological reaction) were added as separate risks since the 2016 Panel meeting, which resulted in changes to the corresponding proposed mitigation measures for the identified risks to health. Additionally, 2016 Panel members suggested we consider including leaching and systemic absorption of antimicrobials or other chemicals as risks. These risks are included within adverse tissue reaction and toxicity and mitigations are included to address them. However, FDA does not believe these need to be added as separate categories of risks to health.

For several of the risks to health, additional mitigation measures are proposed compared to those identified during the 2016 Panel. The proposed mitigations are due to the specific attributes of the materials of the wound dressings and liquid wound washes, which require specific mitigation measures to address the risks identified (e.g., animal-derived materials, botanical extracts). The newly proposed mitigation measures include performance testing and descriptive information and a risk management assessment for animal-derived materials and/or botanical extracts. In addition, certain previously proposed mitigation measures (e.g., labeling, performance data) were recognized to have a role in mitigating more risks than initially proposed during the 2016 Panel meeting. Mitigations have been associated with the relevant identified

risks as subsequently discussed in this proposed rule. Following the 2016 Panel meeting, an additional probable health risk was identified based on reports in the literature (Refs. 49-55) regarding the understood role that our skin microbiota plays in the wound healing cascade.

As such, antimicrobials that leach from wound dressings may inadvertently impact the skin microbiota in the periwound area resulting in impaired wound healing. Antimicrobial preservative claims for wound dressings formulated as a gel, cream, or ointment and liquid wound washes; and protectant and microbial barrier claims for solid wound dressings may be supported by in vitro testing, limiting the stated period of effectiveness to that supported by simulated-use testing parameters, as described in the special controls in section V.D of this proposed rule.

FDA believes that the special controls proposed for these wound dressings and liquid wound washes, in addition to the general controls, mitigate the risks to health discussed in Section V.C, Risks to Health and Public Health Benefits of this proposed rule and are necessary to provide reasonable assurance of safety and effectiveness. Tables 4-6 depict how each identified risk to health would be mitigated by the proposed special controls.

Table 4.--Identified Risks to Health and Proposed Mitigation Measures for Solid Wound Dressings Containing Antimicrobials with a Medium or Low Level of AMR Concern for Protectant Purposes Only and/or Other Chemicals

Identified Risks to Health	Proposed Mitigation Measure(s)
Adverse tissue reaction	• Performance testing and descriptive information • Biocompatibility evaluation • Risk management assessment for the inclusion of animal-derived material and/or botanical extracts • Labeling
Immunological reaction	• Performance testing and descriptive information • Risk management assessment for the inclusion of animal-derived material and/or botanical extracts • Labeling
Transmission of pathogens and parasites (e.g., bacteria, mycoplasma, fungi, viruses, and other transmissible spongiform encephalopathy agents)	• Performance testing and descriptive information • Risk management assessment for the inclusion of animal-derived material • Labeling
Toxicity	• Performance testing and descriptive information • Biocompatibility evaluation • Risk management assessment for the inclusion of animal-derived material and/or botanical extracts

	• Labeling
Delayed wound healing	• Performance testing and descriptive information • Biocompatibility evaluation • Labeling
Incompatibilities with other therapies	• Labeling
Contribution to the spread of antimicrobial resistance (AMR)	• Antimicrobial Characterization and Performance Testing • AMR risk assessment • Labeling
Infection	• Antimicrobial Characterization and Performance Testing • Shelf life validation • Sterilization validation • Risk management assessment for animal-derived materials and/or botanical extracts • Labeling
Microbial growth within the product during use	• Antimicrobial Characterization and Performance Testing • Sterilization validation
Product degradation during stated shelf storage	• Shelf life validation • Labeling
Retention of dressing material in wound	• Performance testing and descriptive information • Labeling
Loss of Barrier function	• Antimicrobial Characterization and Performance Testing
Negatively impacting the skin microbiota in the periwound area resulting in impaired wound healing	• Antimicrobial Characterization and Performance Testing • Labeling

Table 5.--Identified Risks to Health and Proposed Mitigation Measures for Wound Dressings Formulated as a Gel, Cream, or Ointment Containing Antimicrobials with a Medium or Low Level of AMR Concern for Preservative Purposes Only and/or Other Chemicals

Identified Risks to Health	Proposed Mitigation Measure(s)
Adverse tissue reaction	• Performance testing and descriptive information • Biocompatibility evaluation • Risk management assessment for the inclusion of animal-derived material and/or botanical extracts • Labeling
Immunological reaction	• Performance testing and descriptive information • Risk management assessment for the inclusion of animal-derived material and/or botanical extracts • Labeling
Transmission of pathogens and parasites (e.g., bacteria, mycoplasma, fungi, viruses, and other transmissible spongiform encephalopathy agents)	• Performance testing and descriptive information • Risk management assessment for the inclusion of animal-derived material • Labeling
Toxicity	• Performance testing and descriptive information • Biocompatibility evaluation • Risk management assessment for the inclusion of animal-derived material and/or botanical extracts • Labeling
Delayed wound healing	• Performance testing and descriptive information • Biocompatibility evaluation • Labeling

Incompatibilities with other therapies	• Labeling
Contribution to the spread of antimicrobial resistance (AMR)	• Antimicrobial Characterization and Preservative Effectiveness Testing • AMR risk assessment • Labeling
Infection	• Antimicrobial Characterization and Preservative Effectiveness Testing • Shelf life validation • Sterilization validation • Risk management assessment for animal-derived materials and/or botanical extracts • Labeling
Microbial growth within the product during storage	• Antimicrobial Characterization and Preservative Effectiveness Testing • Sterilization validation
Product degradation during stated shelf storage	• Shelf life validation • Labeling
Negatively impacting the skin microbiota in the periwound area resulting in impaired wound healing	• Antimicrobial Characterization and Performance Testing • Labeling

Table 6.--Identified Risks to Health and Proposed Mitigation Measures for Liquid Wound Washes Containing Antimicrobials with a Medium or Low Level of AMR Concern for Preservative Purposes Only, and/or Containing Other Chemicals

Identified Risks to Health	Proposed Mitigation Measure(s)
Adverse tissue reaction	• Performance testing and descriptive information • Biocompatibility evaluation • Risk management assessment for the inclusion of animal-derived material and/or botanical extracts • Labeling
Immunological reaction	• Performance testing and descriptive information • Risk management assessment for the inclusion of animal-derived material and/or botanical extracts • Labeling
Transmission of pathogens and parasites (e.g., bacteria, mycoplasma, fungi, viruses, and other transmissible spongiform encephalopathy agents)	• Performance testing and descriptive information • Risk management assessment for the inclusion of animal-derived material • Labeling
Toxicity	• Performance testing and descriptive information • Biocompatibility evaluation • Risk management assessment for the inclusion of animal-derived material and/or botanical extracts • Labeling
Delayed wound healing	• Performance testing and descriptive information • Biocompatibility evaluation • Labeling
Incompatibilities with other therapies	• Labeling
Contribution to the spread of antimicrobial resistance (AMR)	• Antimicrobial Characterization and Preservative Effectiveness Testing

	• AMR risk assessment • Labeling
Infection	• Antimicrobial Characterization and Preservative Effectiveness Testing • Shelf life validation • Sterilization validation • Risk management assessment for animal-derived materials and/or botanical extracts • Labeling
Microbial growth within the product during storage	• Antimicrobial Characterization and Preservative Effectiveness Testing • Sterilization validation
Product degradation during stated shelf storage	• Shelf life validation • Labeling
Inability to remove wound debris and foreign materials	• Performance testing and descriptive information • Labeling
Negatively impacting the skin microbiota in the periwound area resulting in impaired wound healing	• Antimicrobial Characterization and Performance Testing • Labeling

VI. Proposed Effective/Compliance Dates

FDA proposes that any final rule, based on this proposed rule, become effective 30 days after its date of publication in the *Federal Register*.

Below, FDA has laid out a proposed tiered approach that we believe will help ensure the efficient and effective implementation of this classification regulation, when finalized.

A. Devices That Are Proposed To Be Classified into Class III

For devices proposed to be classified into class III in this proposed rule, FDA is publishing a proposed order to require the filing of a PMA elsewhere in this issue of the *Federal Register*.

If this proposed rule and related proposed order to require the filing of a PMA are finalized, wound dressings and liquid wound washes that are proposed to be classified into class III are considered adulterated if a PMA is not filed with FDA within 30 months after the classification of the device into class III, and commercial distribution of the product must cease (see section 501(f)(2)(B) of the FD&C Act (21 U.S.C. 351(f)(2)(B))).

Moreover, manufacturers must cease distribution of devices upon receiving a not approvable or denial decision rendered on a PMA. In such circumstances, to resume distribution,

these manufacturers must receive PMA approval for their devices. However, the product may be distributed for investigational use only if the requirements of the investigational device exemptions regulations in 21 CFR part 812 are met.

For currently marketed wound dressings and liquid wound washes that are proposed to be classified into class III, FDA is proposing in the above-mentioned proposed order that it does not intend to enforce compliance with the 30-month deadline by which PMAs must be submitted when a notice of intent to file a PMA is submitted within 90 days of the effective date of the order, if finalized. In circumstances when a notice of intent to file is submitted, FDA is proposing that it does not intend to enforce compliance with the 30-month deadline by which PMAs must be submitted when a PMA is submitted within 90 days after the 30-month deadline. However, as discussed above, even if a notice of intent and PMA are submitted by these dates, manufacturers must cease distribution of devices upon receiving a not approvable or denial decision rendered on a PMA.

B. Devices That Are Proposed To Be Classified into Class II

- Devices proposed to be classified into class II that have not been offered for sale prior to the effective date of this rule, when finalized, or have been offered for sale but are required to submit a new 510(k) under § 807.81(a)(3): FDA proposes that before marketing these devices, manufacturers would have to obtain 510(k) clearance (unless exempted from 510(k)), and demonstrate compliance with the applicable special controls, within 6 months after the effective date of this rule, when finalized. After that date, if a manufacturer markets such a device without receiving 510(k) clearance, then FDA would consider taking action against such a manufacturer under its usual enforcement policies.
- Devices proposed to be classified into class II that have prior 510(k) clearance: FDA proposes that it would accept a new 510(k) and would issue a new clearance letter, as appropriate, indicating substantial equivalence and compliance with the special controls. These devices could serve as predicates for new devices. These clearance letters would be

made publicly available in FDA's 510(k) database, and compliance with special controls at the time of clearance would be stated in the publicly available 510(k) Summary posted in this database. FDA believes that our public database is a transparent tool allowing consumers to confirm that their devices have been submitted under a new 510(k) and demonstrate compliance with the applicable special controls.

For the devices proposed to be classified into class II, subject to special controls as described in this proposed rule, FDA proposes that the special controls become effective 6 months after the effective date of the rule, when finalized. FDA proposes that if a manufacturer markets such a device 6 months after the effective date of the rule, when finalized, and that device does not comply with the special controls, then FDA would consider taking action against such a manufacturer under its usual enforcement policies.

VII. Preliminary Economic Analysis of Impact

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, Executive Order 14094, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4).

Executive Orders 12866, 13563, and 14094 direct us to assess all benefits, costs, and transfers of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Rules are "significant" under Executive Order 12866 Section 3(f)(1) (as amended by Executive Order 14094) if they "have an annual effect on the economy of $200 million or more (adjusted every 3 years by the Administrator of the Office of Information and Regulatory Affairs (OIRA) for changes in gross domestic product); or adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local, territorial, or tribal governments or communities." OIRA has determined that this proposed rule is not a significant regulatory action under Executive Order 12866, section 3(f)(1).

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the costs of the proposed rule primarily accrue to larger firms, we propose to certify that the proposed rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes estimates of anticipated impacts, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $177 million, using the most current (2022) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

This proposed rule, if finalized, would classify certain types of currently unclassified wound dressings and liquid wound washes containing antimicrobials and/or other chemicals: solid dressings; wound dressings formulated as a gel, cream, or ointment; and liquid wound washes. FDA is proposing to classify wound dressings and liquid wound washes containing medically important antimicrobials into class III due to their high level of AMR concern, for which FDA is separately proposing to require the filing of a PMA. FDA has determined that general controls and special controls together are insufficient to provide reasonable assurance of safety and effectiveness for such wound dressings and liquid wound washes. In addition, FDA is proposing to classify wound dressings and liquid wound washes containing antimicrobials with a medium or low level of AMR concern into class II subject to general and special controls. FDA is publishing this proposed rule based, in part, on the recommendations of the General and Plastic Surgery Devices Panel regarding the classification of certain types of wound dressings and liquid wound washes.

To estimate costs and benefits associated with the proposed rule, if finalized, we assume that the appropriate baseline is the current state of the United States with unclassified wound dressings and liquid wound washes containing antimicrobials and/or other chemicals. We then compare the likely impacts of the proposed rule against this baseline. The quantifiable benefits of the proposed rule, if finalized, accrue to manufacturers of wound dressings and liquid wound washes and FDA. These benefits are the result of clarifications in the 510(k) submission process, specifically defined regulatory classification, and published special controls. This additional clarity in requirements should result in fewer additional information submissions to FDA.

We estimate annualized cost savings ranging from approximately $1.12 million to $6.31 million at a 3 percent discount rate, and approximately $1.14 million to $6.42 million at a 7 percent discount rate. Our primary annualized estimates are approximately $2.66 million at a 3 percent discount rate and $2.71 million at a 7 percent discount rate. The primary estimates of the present value of total cost savings in the 10 years following any final rule that may be issued based on this proposed rule are $24.55 million at a 3 percent rate of discount and $19.02 million at a 7 percent rate of discount. If the proposed rule is finalized, society may experience welfare gains from reductions in AMR due to the rule. These welfare gains would be in the form of decreased mortality, morbidity, and medical costs. Unfortunately, the magnitude of these potential benefits is difficult to forecast, and we do not quantify these impacts in the analysis. We summarize quantified benefits in table 7.

The costs of the proposed rule, if finalized, are associated with costs to industry for reading and understanding the rule, preparing and submitting PMAs, and other costs related to the PMA process and maintaining the class III designation. FDA also incurs costs from reviewing PMAs, annual and supplemental reports, and inspection activities. When annualized over a period of 10 years, we estimate these costs range from approximately $0.72 million to $1.25 million at a 3 percent discount rate, and approximately $0.65 million to $1.17 million at a 7 percent discount rate. Our primary annualized estimates are approximately $0.92 million at a 3

percent discount rate and $0.85 million at a 7 percent discount rate. The primary estimates of the present value of total costs in the 10 years following any final rule that may be issued based on the proposed rule are approximately $7.23 million at a 3 percent discount rate and $6.48 million at a 7 percent discount rate. These values are summarized in table 7.

Table 7.--Summary of Benefits, Costs, and Distributional Effects of Proposed Rule

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized $millions/year	$2.71	$1.14	$6.42	2022	7%	10 years	
		$2.66	$1.12	$6.31	2022	3%	10 years	
	Annualized Quantified					7%		
						3%		
	Qualitative							
Costs	Annualized Monetized $millions/year	$0.92	$0.72	$1.25	2022	7%	10 years	
		$0.85	$0.65	$1.17	2022	3%	10 years	
	Annualized Quantified					7%		
						3%		
	Qualitative							
Transfers	Federal Annualized Monetized $millions/year					7%		
						3%		
	From/To	From:			To:			
	Other Annualized Monetized $millions/year	$0.30	$0.19	$0.58	2022	7%	10 years	
		$0.28	$0.18	$0.56	2022	3%	10 years	
	From/To	From: Industry			To: FDA			
Effects	State, Local, or Tribal Government: None Small Business: None Wages: Growth:							

We have developed a comprehensive Preliminary Economic Analysis of Impacts that assesses the impacts of the proposed rule. The full preliminary analysis of economic impacts is available in the docket for this proposed rule (Ref. 56) and at https://www.fda.gov/about-fda/economics-staff/regulatory-impact-analyses-ria.

VIII. Analysis of Environmental Impact

We have determined under 21 CFR 25.34(b) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IX. Paperwork Reduction Act of 1995

FDA tentatively concludes that this proposed rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

X. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that this proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

XI. Consultation and Coordination with Indian Tribal Governments

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13175. We have tentatively determined that the rule does not contain policies that would have a substantial direct effect on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the Federal Government and Indian Tribes. The Agency solicits comments from tribal officials on any potential impact on Indian Tribes from this proposed action.

XII. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at https://www.regulations.gov. References without asterisks are not on public display at https://www.regulations.gov because they have copyright restriction. Some may be available at

the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. FDA has verified the website addresses, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

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List of Subjects in 21 CFR Part 878

Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, we propose that 21 CFR part 878 be amended as follows:

PART 878 – GENERAL AND PLASTIC SURGERY DEVICES

1. The authority citation for part 878 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 360l, 371.

2. Add § 878.4016 to subpart E to read as follows:

§ 878.4016 Solid wound dressings containing antimicrobials and/or other chemicals.

(a) *Identification*. A solid wound dressing containing antimicrobials and/or other chemicals that are in a category listed in paragraph (a)(2) of this section is used to cover and protect a wound, to absorb exudate, and to maintain appropriate moisture balance within the wound and is intended for use only on external cutaneous (skin) wounds. The solid wound dressing materials are resorbable or nonresorbable, synthetic or naturally derived materials (including animal-derived materials such as collagen or chitosan), which are provided sterile in a form able to hold structural integrity temporarily or permanently. This regulation does not include a solid wound dressing that contains only animal-derived materials without the presence of antimicrobials and/or other chemicals.

(1) Antimicrobials are used for protectant purposes only to reduce microbial growth within the solid wound dressing while in use, or to provide an antimicrobial barrier to microbial penetration through the solid wound dressing;

(2) Categories of other chemicals are wound protectants, honey, synthetic peptides, or botanical extracts.

(b) *Classification*. (1) Class III (premarket approval) for solid wound dressings that are identified in paragraph (a) of this section and that contain one or more medically important antimicrobials acting as protectants.

(i) *Date premarket approval application is required*. A PMA is required to be filed with the Food and Drug Administration on or before [DATE OF THE LAST DAY OF THE 30TH FULL CALENDAR MONTH AFTER EFFECTIVE DATE OF FINAL RULE], for any solid wound dressing, as identified in paragraph (a) of this section, that either contains one or more medically important antimicrobials acting as protectants and was in commercial distribution before May 28, 1976, or has, on or before [DATE OF THE LAST DAY OF THE 30TH FULL CALENDAR MONTH AFTER EFFECTIVE DATE OF FINAL RULE], been found to be substantially equivalent to any solid wound dressing, as identified in paragraph (a) of this section, that contains one or more medically important antimicrobials and that was in commercial distribution before May 28, 1976. Any other solid wound dressing, as identified in paragraph (a) of this section, that contains one or more medically important antimicrobials shall have an approved PMA in effect before being placed in commercial distribution.

(ii) [Reserved]

(2) Class II (special controls) for solid wound dressings that are identified in paragraph (a) of this section and that contain one or more antimicrobials acting as protectants with a medium or low level of antimicrobial resistance (AMR) concern and/or other chemicals. The special controls are:

(i) *Performance testing and descriptive information.* Performance testing and descriptive information must demonstrate the functionality of the solid wound dressing to achieve the specified use, including:

(A) The physical and chemical characteristics of the solid wound dressing must be established. The following must be provided:

(1) Identity, quantification, and purpose of each component in the finished product;

(2) Specifications and characterization of each component in the finished product;

(3) Demonstration that each component has a purpose and is present in appropriate amounts to perform as intended under anticipated conditions of use, including evaluation of expected worst-case conditions; and

(4) Final release specifications for the manufactured solid wound dressing.

(B) The solid wound dressing must be demonstrated to be sterile and the sterilization process must be validated.

(C) The solid wound dressing must be demonstrated to be biocompatible.

(D) Bench performance testing data must demonstrate that the solid wound dressing performs as intended under anticipated conditions of use, including evaluation of expected worst-case conditions.

(E) Performance data must support the shelf life of the solid wound dressing by demonstrating package integrity and product functionality over the identified shelf life.

(ii) *Antimicrobial characterization and performance testing*. For solid wound dressings containing antimicrobials with a medium or low level of AMR concern, antimicrobial characterization and performance testing must address the following:

(A) Performance data must demonstrate that the antimicrobial has a purpose and is present in appropriate amounts to perform as intended under anticipated conditions of use and storage conditions, including evaluation of worst-case conditions. If the antimicrobial is present as a microbial barrier to cover and protect a wound, microbial barrier testing must be conducted to demonstrate elimination of passage of microorganisms through the solid wound dressing. If the antimicrobial is present to inhibit microbial growth within the solid wound dressing being used to cover and protect a wound, antimicrobial effectiveness testing must be conducted to demonstrate inhibition of microbial growth within the solid wound dressing during use. This testing must include:

(1) Establishment of the Minimum Effective Concentration (MEC) of the antimicrobial in the context of the final solid wound dressing under worst-case conditions.

(2) Identification of the period of effectiveness (i.e., maximum product use life) based on concentration of antimicrobial, leachability data, and performance under worst-case simulated use conditions.

(3) For the tests conducted, evaluation with clinically relevant microbial species, including available strains of challenge organisms containing specific antimicrobial resistance mechanisms as part of worst-case scenario performance testing.

(B) Evaluation and identification of any probable risks for probable contributions to the development and spread of antimicrobial resistance must be provided, and must include:

(1) Identification of the antimicrobial, proposed mechanism(s) of action, and expected spectrum of activity; and

(2) An AMR assessment for each antimicrobial component, including the following characterization elements based on literature review:

(i) Known resistance mechanisms;

(ii) Transmissibility of resistance mechanisms;

(iii) List of resistant microbial species; and

(iv) Potential for coselection (e.g., via coresistance or cross-resistance) for medically important antimicrobial resistance mechanisms.

(iii) If the solid wound dressing contains animal-derived material(s), data must include:

(A) A risk management assessment for the inclusion of animal-derived material(s) which considers any probable risk associated with the presence of the animal tissue in the final finished solid wound dressing (including pathogen and parasite infection and immunological reaction). The risk management assessment must describe how these risks are controlled and mitigated by:

(1) Documentation of the processing methods, including methods of animal husbandry and tissue selection as well as methods for tissue handling, storage, transport, and quarantine, that mitigate the risk of parasites and pathogens.

(2) Performance data which demonstrates the ability of the manufacturing and sterilization procedures to ensure the adequate removal (i.e., clearance or inactivation) of parasites and pathogens (including bacteria, mycoplasma, fungi, virus, and transmissible spongiform encephalopathy agents) from the final finished solid wound dressing.

(B) If the device contains materials derived from a new animal species or from manufacturing processes which cause structural changes (i.e., denaturation, modification) to the animal protein, performance data (e.g., patch and prick testing, human repeat insult patch testing) must demonstrate that the device is not immunogenic.

(iv) If the solid wound dressing contains a botanical extract, additional supporting data must include:

(A) A risk management assessment for including the botanical extract in the solid wound dressing which considers any probable risk associated with the presence of the botanical extract in the final finished solid wound dressing.

(B) The risk management assessment must describe how these risks are controlled and mitigated by providing the following:

(*1*) The chemical composition of the botanical extract, including the identity and quantification of the chemical constituents and impurities (e.g., elemental impurities, residual solvents and pesticides, microbial contaminants, adventitious toxins, and degradation products) and the lot-to-lot consistency of the botanical extract within the final finished solid wound dressing.

(*2*) Documentation of the botanical extract function and activities after topical application. Such information must describe the purpose of the botanical extract in the solid

wound dressing and how it is present in appropriate amounts to perform as intended under anticipated conditions of use, including expected worst-case conditions.

(*3*) Identification of any probable risk to health from use of the botanical extract and how these risks were evaluated and are mitigated via the botanical concentration in the final product, duration of body contact, manufacturing and process controls, performance data, and labeling for the solid wound dressing.

(v) The labeling must include:

(A) A description of the intended user population;

(B) Specific instructions regarding the proper placement, sizing, duration of use for the solid wound dressing, frequency of use, and removal of the solid wound dressing, if applicable;

(C) A list of each ingredient or component within the solid wound dressing, including the functional role of that ingredient within the solid wound dressing;

(D) A warning statement regarding any incompatibilities with other therapies;

(E) A warning statement regarding the potential for the development of infection, including signs of an infection and a description of the steps to take in case of infection;

(F) If the solid wound dressing is nonresorbable, a warning statement for the potential retention of material in the wound or the surrounding area;

(G) A contraindication for any known sensitivity to components within the product;

(H) A shelf life (i.e., maximum period the unopened solid wound dressing is stable while stored on the shelf under a specified range of environmental conditions);

(I) A maximum use life per application of solid wound dressing (i.e., period the solid wound dressing is recommended for use prior to removal);

(J) A statement regarding when to discontinue use of the solid wound dressing after multiple reapplications based on biocompatibility and performance testing; and

(K) For solid wound dressings indicated for over-the-counter use, a statement specifying conditions, uses, or purposes for which the product may be safely administered by a lay user without the supervision of a licensed practitioner.

(vi) If the solid wound dressing contains an antimicrobial, the labeling must also include:

(A) Statement of the role of the antimicrobial in the product.

(B) A warning statement regarding the potential for selection of antibiotic resistant organisms if the wound dressing contains an antimicrobial with a medium level of AMR concern.

(C) Specific instructions regarding how and when to properly dispose of the product.

(D) A statement of general effectiveness, such as "antimicrobial," "antibacterial," or "microbial barrier," without listing specific test organisms or log reduction values.

(E) A statement explaining that the effectiveness of the antimicrobial in affecting wound bioburden has not been evaluated or established.

(F) A warning statement regarding the potential for the antimicrobial to leach from the dressing and negatively impact the skin microbiota in the periwound area which may result in impaired wound healing.

(vii) Any statements in the labeling must be clear such that they may be understood by the end user, supported by appropriate evidence, and consistent with the intended use of covering and protecting a wound, absorbing exudate, and maintaining appropriate moisture balance within the wound.

3. Add § 878.4017 to subpart E to read as follows:

§ 878.4017 Wound dressings formulated as a gel, cream, or ointment containing antimicrobials and/or other chemicals.

(a) *Identification*. A wound dressing formulated as a gel, cream, or ointment containing antimicrobials and/or other chemicals that are in a category listed in paragraph (a)(2) of this

section is used to maintain appropriate moisture balance within the wound and is intended for use only on external cutaneous (skin) wounds. The wound dressing materials are synthetic or naturally derived materials (including animal-derived materials such as collagen or chitosan). Wound dressings formulated as a gel, cream, or ointment containing antimicrobials and/or other chemicals are amorphous and can have high water content with thickening agents or consist of an oil-water emulsion. This regulation does not include a wound dressing formulated as a gel, cream, or ointment that contains only animal-derived materials without the presence of antimicrobials and/or other chemicals.

(1) Antimicrobials are used for preservative purposes only to maintain shelf life for a nonsterile wound dressing or a multiple-use wound dressing for single patient use only;

(2) Categories of other chemicals are wound protectants, honey, synthetic peptides, or botanical extracts.

(b) *Classification*. (1) Class III (premarket approval) for wound dressings formulated as a gel, cream, or ointment that are identified in paragraph (a) of this section and that contain one or more medically important antimicrobials acting as preservatives.

(i) *Date premarket approval application is required*. A PMA is required to be filed with the Food and Drug Administration on or before [DATE OF THE LAST DAY OF THE 30TH FULL CALENDAR MONTH AFTER EFFECTIVE DATE OF FINAL RULE], for any wound dressing formulated as a gel, cream, or ointment, as identified in paragraph (a) of this section, that either contains one or more medically important antimicrobials acting as preservatives and was in commercial distribution before May 28, 1976, or has, on or before [DATE OF THE LAST DAY OF THE 30TH FULL CALENDAR MONTH AFTER EFFECTIVE DATE OF FINAL RULE], been found to be substantially equivalent to any wound dressing formulated as a gel, cream, or ointment, as identified in paragraph (a) of this section, that contains one or more medically important antimicrobials and that was in commercial distribution before May 28, 1976. Any other wound dressing formulated as a gel, cream, or ointment, as identified in

paragraph (a) of this section, that contains one or more medically important antimicrobials shall have an approved PMA in effect before being placed in commercial distribution.

(ii) [Reserved]

(2) Class II (special controls) for wound dressings formulated as a gel, cream, or ointment that are identified in paragraph (a) of this section and that contain one or more antimicrobials acting as preservatives with a medium or low level of AMR concern and/or other chemicals. The special controls are:

(i) *Performance testing and descriptive information.* Performance testing and descriptive information must demonstrate the functionality of the wound dressing formulated as a gel, cream, or ointment to achieve the specified use, including:

(A) The physical and chemical characteristics of the wound dressing formulated as a gel, cream, or ointment must be established. The following must be provided:

(*1*) Identity, quantification, and purpose of each component in the finished product;

(*2*) Specifications and characterization of each component in the finished product;

(*3*) Demonstration that each component has a purpose and is present in appropriate amounts to perform as intended under anticipated conditions of use, including evaluation of expected worst-case conditions; and

(*4*) Final release specifications for the manufactured wound dressing formulated as a gel, cream, or ointment.

(B) If labeled as sterile, the wound dressing formulated as a gel, cream, or ointment must be demonstrated to be sterile and the sterilization process must be validated. If labeled as nonsterile, performance data must demonstrate that the product may not be sterilized by established sterilization methods and each manufactured lot of product has an acceptable bioburden level that is maintained throughout the stated shelf life.

(C) The wound dressing formulated as a gel, cream, or ointment must be demonstrated to be biocompatible.

(D) Bench performance testing data must demonstrate that the wound dressing formulated as a gel, cream, or ointment performs as intended under anticipated conditions of use, including evaluation of expected worst-case conditions.

(E) Performance data must support the shelf life of the wound dressing formulated as a gel, cream, or ointment by demonstrating package integrity and product functionality over the identified shelf life. If the product is intended for multiple uses after opening, continued low bioburden, product stability, and functionality over the identified use life must be demonstrated.

(ii) *Antimicrobial characterization and preservative effectiveness testing*. For wound dressings formulated as a gel, cream, or ointment containing antimicrobials with a medium or low level of AMR concern, antimicrobial characterization and preservative effectiveness testing must address the following:

(A) Performance data must demonstrate that the antimicrobial has a purpose and is present in appropriate amounts to perform as intended under anticipated conditions of use and storage conditions, including evaluation of worst-case conditions. This testing must include:

(*1*) Establishment of the MEC of the antimicrobial in the context of the final wound dressing formulated as a gel, cream, or ointment.

(*2*) Identification of the period of preservative effectiveness for multiple-use products (i.e., after the product has been opened) based on concentration of antimicrobial and preservative effectiveness testing under worst-case simulated use conditions.

(*3*) Preservative effectiveness testing must be conducted on at least three different manufactured lots of the final, finished device that has been real-time aged for the stated shelf life. If the dressing is a multiple-use product, the test articles should also be conditioned based on worst-case simulated use for maximum use life.

(*4*) For nonsterile products, information should be provided regarding the characterization of bioburden within the product.

(B) Evaluation and identification of any probable risks for probable contributions to the development and spread of antimicrobial resistance must be provided, and must include:

(*1*) Identification of the antimicrobial, proposed mechanism(s) of action, and expected spectrum of activity; and

(*2*) An AMR assessment for each antimicrobial component, including the following characterization elements based on literature review:

(*i*) Known resistance mechanisms;

(*ii*) Transmissibility of resistance mechanisms;

(*iii*) List of resistant microbial species; and

(*iv*) Potential for coselection (e.g., via coresistance or cross-resistance) for medically important antimicrobial resistance mechanisms.

(iii) If the wound dressing formulated as a gel, cream, or ointment contains animal-derived material(s), data must include:

(A) A risk management assessment for the inclusion of animal-derived material(s) which considers any probable risk associated with the presence of the animal tissue in the final finished wound dressing formulated as a gel, cream, or ointment (including pathogen and parasite infection and immunological reaction). The risk management assessment must describe how these risks are controlled and mitigated by:

(*1*) Documentation of the processing methods, including animal husbandry and tissue selection as well as methods for tissue storage, transport, and quarantine, that mitigate the risk of parasites and pathogens.

(*2*) Performance data which demonstrates the ability of the manufacturing and sterilization procedures to ensure the adequate removal (i.e., clearance or inactivation) of parasites and pathogens (including bacteria, mycoplasma, fungi, virus, and transmissible spongiform encephalopathy agents) from the final finished wound dressing formulated as a gel, cream, or ointment.

(B) If the device contains materials derived from a new animal species or from manufacturing processes which cause structural changes (i.e., denaturation, modification) to the animal protein, performance data (e.g., patch and prick testing, human repeat insult patch testing) must demonstrate that the device is not immunogenic.

(iv) If the wound dressing formulated as a gel, cream, or ointment contains a botanical extract, additional supporting data must include:

(A) A risk management assessment for including the botanical extract in the wound dressing formulated as a gel, cream, or ointment which considers any probable risk associated with the presence of the botanical extract in the final finished wound dressing formulated as a gel, cream, or ointment.

(B) The risk management assessment must describe how these risks are controlled and mitigated by providing the following:

(*1*) The chemical composition of the botanical extract, including the identity and quantification of the chemical constituents and impurities (e.g., elemental impurities, residual solvents and pesticides, microbial contaminants, adventitious toxins, and degradation products), and the lot-to-lot consistency of the botanical extract within the final finished wound dressing formulated as a gel, cream, or ointment.

(*2*) Documentation of the botanical extract function and activities after topical application. Such information must describe the purpose of the botanical extract in the wound dressing formulated as a gel, cream, or ointment and how it is present in appropriate amounts to perform as intended under anticipated conditions of use, including expected worst-case conditions.

(*3*) Identification of any probable risk to health from use of the botanical extract and how these risks were evaluated and are mitigated via the botanical concentration in the final product, duration of body contact, manufacturing and process controls, performance data, and labeling for the wound dressing formulated as a gel, cream, or ointment.

(v) The labeling must include:

(A) A description of the intended user population;

(B) Specific instructions regarding the proper application of the product, duration of use for the wound dressing, frequency of use, and instructions regarding the removal of the product residuals prior to reapplication, if applicable;

(C) A list of each ingredient or component within the wound dressing, including the functional role of that ingredient within the wound dressing;

(D) A warning statement regarding any incompatibilities with other therapies;

(E) A warning statement regarding the potential for the development of infection, including signs of an infection and a description of the steps to take in case of infection;

(F) A contraindication for any known sensitivity to components within the product;

(G) A shelf life (i.e., maximum period the unopened wound dressing formulated as a gel, cream, or ointment is stable while stored on the shelf under a specified range of environmental conditions);

(H) The maximum period of use (including reapplications) based on biocompatibility and performance testing; and

(I) For wound dressings formulated as a gel, cream, or ointment indicated for over-the-counter use, a statement specifying conditions, uses, or purposes for which the product may be safely administered by a lay user without the supervision of a licensed practitioner.

(vi) If the wound dressing formulated as a gel, cream, or ointment contains an antimicrobial, the labeling must also include:

(A) Statement of the role of the antimicrobial in the product.

(B) A warning statement regarding the potential for selection of antibiotic resistant organisms if the wound dressing contains an antimicrobial with a medium level of AMR concern.

(C) Specific instructions regarding how and when to properly dispose of the product.

(D) A statement of general effectiveness, such as “antimicrobial,” “antibacterial,” or “microbial barrier,” without listing specific test organisms or log reduction values.

(E) A statement explaining that the effectiveness of the antimicrobial in affecting wound bioburden has not been evaluated or established.

(F) A warning statement regarding the potential for the antimicrobial to leach from the dressing and negatively impact the skin microbiota in the periwound area which may result in impaired wound healing.

(vii) Any statements in the labeling must be clear such that they may be understood by the end user, supported by appropriate evidence, and consistent with the intended use of maintaining appropriate moisture balance within the wound.

4. Add § 878.4019 to subpart E to read as follows:

§ 878.4019 Liquid wound washes.

(a) *Identification*. A liquid wound wash containing antimicrobials and/or other chemicals that are in a category listed in paragraph (a)(2) of this section is a water-based solution used to mechanically irrigate and physically remove debris from external wounds and intended for use on external cutaneous (skin) wounds. It is also used to moisten solid wound dressings to maintain appropriate moisture balance within the dressing. This regulation does not include liquid wound washes that contain only animal-derived materials without the presence of antimicrobials and/or other chemicals.

(1) Antimicrobials are used for preservative purposes only to maintain shelf life for a nonsterile liquid wound wash or a multiple-use liquid wound wash for single patient use only;

(2) Categories of other chemicals are wound protectants, honey, synthetic peptides, or botanical extracts.

(b) *Classification*. (1) Class III (premarket approval) for liquid wound washes that are identified in paragraph (a) of this section and that contain one or more medically important antimicrobials acting as preservatives.

(i) *Date premarket approval application is required*. A PMA is required to be filed with the Food and Drug Administration on or before [DATE OF THE LAST DAY OF THE 30TH FULL CALENDAR MONTH AFTER EFFECTIVE DATE OF FINAL RULE], for any liquid wound wash, as identified in paragraph (a) of this section, that either contains one or more medically important antimicrobials and was in commercial distribution before May 28, 1976, or has, on or before [DATE OF THE LAST DAY OF THE 30TH FULL CALENDAR MONTH AFTER EFFECTIVE DATE OF FINAL RULE], been found to be substantially equivalent to any liquid wound wash, as identified in paragraph (a) of this section, that contains one or more medically important antimicrobials and that was in commercial distribution before May 28, 1976. Any other liquid wound wash, as identified in paragraph (a) of this section, that contains one or more medically important antimicrobials shall have an approved PMA in effect before being placed in commercial distribution.

(ii) [Reserved]

(2) Class II (special controls) for liquid wound washes that are identified in paragraph (a) of this section and that contain one or more antimicrobials acting as preservatives with a medium or low level of AMR concern and/or other chemicals or when containing water or 0.9 percent saline only. The special controls for this device are:

(i) *Performance testing and descriptive information.* Performance testing and descriptive information must demonstrate the functionality of the liquid wound wash to achieve the specified use, including:

(A) The physical and chemical characteristics of the liquid wound wash must be established. The following must be provided:

(*1*) Identity, quantification, and purpose of each component in the finished product;

(*2*) Specifications and characterization of each component in the finished product;

(*3*) Demonstration that each component has a purpose and is present in appropriate amounts to perform as intended under anticipated conditions of use, including evaluation of expected worst-case conditions; and

(*4*) Final release specifications for the manufactured liquid wound wash.

(B) If labeled as sterile, the liquid wound wash must be demonstrated to be sterile and the sterilization process must be validated. If labeled as nonsterile, performance data must demonstrate that the product may not be sterilized by established sterilization methods and each manufactured lot of product has an acceptable bioburden level that is maintained throughout the stated shelf life.

(C) The liquid wound wash must be demonstrated to be biocompatible.

(D) Bench performance testing data must demonstrate that the liquid wound wash performs as intended under anticipated conditions of use, including evaluation of expected worst-case conditions.

(F) Performance data must support the shelf life of the liquid wound wash by demonstrating package integrity and product functionality over the identified shelf life. If the product is intended for multiple uses after opening, continued low bioburden, product stability, and functionality over the identified use life must be demonstrated.

(ii) *Antimicrobial characterization and preservative effectiveness testing*. For liquid wound washes containing antimicrobials with a medium or low level of AMR concern, antimicrobial characterization and preservative effectiveness testing must address the following:

(A) Performance data must demonstrate that the antimicrobial has a purpose and is present in appropriate amounts to perform as intended under anticipated conditions of use and storage conditions, including evaluation of worst-case conditions. This testing must include:

(*1*) Establishment of the MEC of the antimicrobial in the context of the final liquid wound wash.

(*2*) Identification of the period of preservative effectiveness for multiple-use products (i.e., after the product has been opened) based on concentration of antimicrobial and preservative effectiveness testing under worst-case simulated use conditions.

(*3*) Preservative effectiveness testing must be conducted on at least three different manufactured lots of the final, finished device that has been real-time aged for the stated shelf life. If the liquid wound wash is a multiple-use product, the test articles should also be conditioned based on worst-case simulated use for maximum use life.

(*4*) For nonsterile products, information should be provided regarding the characterization of bioburden within the product.

(B) Evaluation and identification of any probable risks for probable contributions to the development and spread of antimicrobial resistance must be provided, and must include:

(*1*) Identification of the antimicrobial, proposed mechanism(s) of action, and expected spectrum of activity; and

(*2*) An AMR assessment for each antimicrobial component, including the following characterization elements based on literature review:

(*i*) Known resistance mechanisms;

(*ii*) Transmissibility of resistance mechanisms;

(*iii*) List of resistant microbial species; and

(*iv*) Potential for coselection (e.g., via coresistance or cross-resistance) for medically important antimicrobial resistance mechanisms.

(iii) If the liquid wound wash contains animal-derived material(s), data must include:

(A) A risk management assessment for the inclusion of animal-derived material(s) which considers any probable risk associated with the presence of the animal tissue in the final finished liquid wound wash (including pathogen and parasite infection and immunological reaction). The risk management assessment must describe how these risks are controlled and mitigated by:

(*1*) Documentation of the processing methods, including animal husbandry and tissue selection as well as methods for tissue storage, transport, and quarantine, that mitigate the risk of parasites and pathogens.

(*2*) Performance data which demonstrates the ability of the manufacturing and sterilization procedures to ensure the adequate removal (i.e., clearance or inactivation) of parasites and pathogens (including bacteria, mycoplasma, fungi, virus, and transmissible spongiform encephalopathy agents) from the final finished liquid wound wash.

(B) If the device contains materials derived from a new animal species or from manufacturing processes which cause structural changes (i.e., denaturation, modification) to the animal protein, performance data (e.g., patch and prick testing, human repeat insult patch testing) must demonstrate that the device is not immunogenic.

(iv) If the liquid wound wash contains a botanical extract, additional supporting data must include:

(A) A risk management assessment for including the botanical extract in the liquid wound wash which considers any probable risk associated with the presence of the botanical extract in the final finished liquid wound wash.

(B) The risk management assessment must describe how these risks are controlled and mitigated by providing the following:

(*1*) The chemical composition of the botanical extract, including the identity and quantification of the chemical constituents and impurities (e.g., elemental impurities, residual solvents and pesticides, microbial contaminants, adventitious toxins, and degradation products), and the lot-to-lot consistency of the botanical extract within the final finished liquid wound wash.

(*2*) Documentation of the botanical extract function and activities after topical application. Such information must describe the purpose of the botanical extract in the liquid

wound wash and how it is present in appropriate amounts to perform as intended under anticipated conditions of use, including expected worst-case conditions.

(*3*) Identification of any probable risk to health from use of the botanical extract and how these risks were evaluated and are mitigated via the botanical concentration in the final product, duration of body contact, manufacturing and process controls, performance data, and labeling for the liquid wound wash.

(v) The labeling must include:

(A) A description of the intended user population;

(B) Specific instructions regarding the proper application of the product, duration of use for the liquid wound wash, and frequency of use if labeled for a period of multiple use;

(C) A list of each ingredient or component within the liquid wound wash, including the functional role of that ingredient within the liquid wound wash;

(D) A warning statement regarding any incompatibilities with other therapies;

(E) A warning statement regarding the potential for the development of infection, including signs of an infection and a description of the steps to take in case of infection;

(F) A contraindication for any known sensitivity to components within the product;

(G) A shelf life (i.e., maximum period the unopened liquid wound wash is stable while stored on the shelf under a specified range of environmental conditions);

(H) A maximum period of use (including reapplications) based on biocompatibility and performance testing.

(I) For liquid wound washes indicated for over-the-counter use, a statement specifying conditions, uses, or purposes for which the product may be safely administered by a lay user without the supervision of a licensed practitioner.

(vi) If the liquid wound wash contains an antimicrobial, the labeling must also include:

(A) Statement of the role of the antimicrobial in the product as a preservative.

(B) A warning statement regarding the potential for selection of antibiotic resistant organisms if the liquid wound wash contains an antimicrobial with a medium level of AMR concern.

(C) Specific instructions regarding how and when to properly dispose of the product.

(D) A statement of general effectiveness, such as “antimicrobial,” “antibacterial,” or “microbial barrier,” without listing specific test organisms or log reduction values.

(E) A statement explaining that the effectiveness of the antimicrobial in affecting wound bioburden has not been evaluated or established.

(F) A warning statement regarding the potential for the antimicrobial to leach from the dressing and negatively impact the skin microbiota in the periwound area which may result in impaired wound healing.

(vii) Any statements in the labeling must be clear such that they may be understood by the end user, supported by appropriate evidence, and consistent with the intended use of mechanically irrigating a wound or maintaining appropriate moisture balance within a solid wound dressing.

Dated: November 21, 2023.

Robert M. Califf,

Commissioner of Food and Drugs.

[FR Doc. 2023-26209 Filed: 11/29/2023 8:45 am; Publication Date: 11/30/2023]